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=> file casreact
FILE 'CASREACT' ENTERED AT 14:28:06 ON 16 SEP 2004
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FILE CONTENT:1840 - 12 Sep 2004 VOL 141 ISS 11

************************************************************
*                                                          *
*     CASREACT now has more than  8 million reactions      *
*                                                          *
************************************************************

Some CASREACT records are derived from the ZIC/VINITI database (1974-1991)
provided by InfoChem, INPI data prior to 1986, and Biotransformations
database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> d que
L1             3 SEA FILE=CASREACT S(W)AMLODIPINE OR R(W)AMLODIPINE


=> d l1 1-3 ibib abs fcrd


L1   ANSWER 1 OF 3  CASREACT  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         140:287273  CASREACT
TITLE:                    A process for the preparation of (S)-(-)-
                          amlodipine nicotinate and its hydrates as
                          antihypertensive agents with improved activity and
                          photostability
INVENTOR(S):              Chung, You-Sup; Ha, Mun-Choun
PATENT ASSIGNEE(S):       Hanlim Pharmaceutical Co., Ltd., S. Korea
SOURCE:                   PCT Int. Appl., 25 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     WO 2004024690      A1   20040325      WO 2003-KR1850   20030908
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,
             PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
             TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
             NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
             GW, ML, MR, NE, SN, TD, TG
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PRIORITY APPLN. INFO.: KR 2002-54809 20020911
KR 2003-1260 20030109

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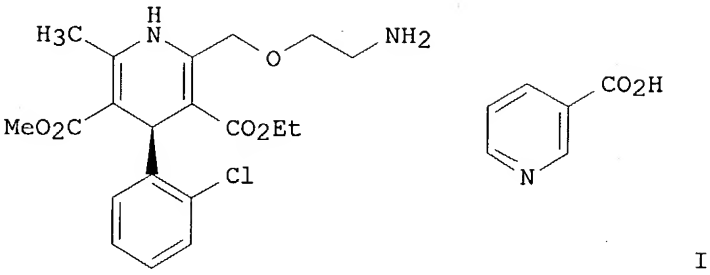

I

AB The dihydrate of (**S**)-(-)-**amlodipine** nicotinate I is prepd. as a form of (**S**)-(-)-**amlodipine** with improved antihypertensive activity and improved photostability. (**S**)-(-)-**amlodipine** in 95% methylated spirit is added to a slurry of nicotinic acid in 95% methylated spirit, slowly heated to reflux and stirred for five hours, and cooled to 5.degree. to form crystals which are washed with isopropanol; dissoln. of the salt in a 95:5 mixt. by mass (90:10 mixt. by vol.) of isopropanol and methanol, stirred at room temp. and slowly cooled to 0.degree. to yield the dihydrate of I as a ppt. I.bul.2H2O is found to be stable for three weeks under a 100 W incandescent bulb 30 cm. away, while (**S**)-(-)-**amlodipine** besylate absorbs water and changes color under the same conditions. I is slightly more active as an antihypertensive agent than racemic amlodipine nicotinate. The anhyd. and unspecified hydrate forms of I are also claimed. I and its hydrated forms are claimed as antiischemic and antihypertensive agents.
NO HIGHLIGHTING INFORMATION PRESENT
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 2 OF 3 CASREACT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 140:287272 CASREACT
TITLE: Process for the preparation of (**S**)-(-)-**amlodipine** by resolution of (RS)-amlodipine with L-tartaric acid
INVENTOR(S): Chung, You-Sup; Ha, Mun-Choun
PATENT ASSIGNEE(S): Hanlim Pharmaceutical Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024689	A1	20040325	WO 2003-KR1849	20030908

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,

TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: KR 2002-54808 20020911

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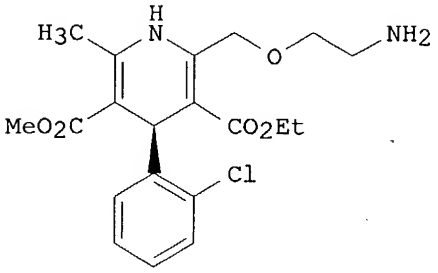

I

AB (**S**)-(-)-**amlodipine** I is prepd. from racemic amlodipine by a resoln. using L-(+)-tartaric acid; L-tartaric acid is much less expensive than the D-tartaric acid used in a previous method for the prepn. of I, decreasing the cost of resoln. and making resoln. of I more amenable to industrial scale synthesis. 0.5-0.55 Equiv. of L-(+)-tartaric acid in DMSO is added to racemic I in DMSO and stirred overnight at room temp. to yield a slurry from which the ppt. is filtered; addn. of methylene chloride to the filtered soln., stirring at ambient temp. for 40 h, cooling to 5.degree. and stirring for two hours yields a ppt. of the DMSO solvate of the L-hemitartrate salt of I. The amt. of DMSO present in the resoln. step should be between four to six times (preferably five times) the vol. of one gram of racemic amlodipine per g of amlodipine resolved, and the amt. of methylene chloride added afterwards should be one to two times the amt. of DMSO present. The DMSO solvate of the L-hemitartrate salt of I can be converted to the hydrate of the L-hemitartrate salt of I by refluxing in methanol to dissolve the DMSO solvate followed by overnight stirring and filtration. Treatment of a methylene chloride soln. of either the DMSO solvate of the L-hemitartrate salt of I or the hydrate of the L-hemitartrate salt of I with a 2 M soln. of sodium bicarbonate in water followed by cooling to 5.degree. and filtration yields I. I is prepd. on gram scale by this method.
NO HIGHLIGHTING INFORMATION PRESENT

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 3 OF 3 CASREACT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 136:369612 CASREACT
TITLE: Preparation of an amlodipine/atorvastatin amide prodrug for the treatment of atherosclerosis, angina pectoris, hypertension, hyperlipidemia and management of cardiac risk.
INVENTOR(S): Crook, Robert J.; Pettman, Alan J.
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1205477	A1	20020515	EP 2001-309169	20011030
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2002082282	A1	20020627	US 2001-985	20011031
US 6737430	B2	20040518		
BR 2001005080	A	20020625	BR 2001-5080	20011108
JP 2002179675	A2	20020626	JP 2001-344576	20011109
PRIORITY APPLN. INFO.:			GB 2000-27410	20001109
			US 2000-255025P	20001212

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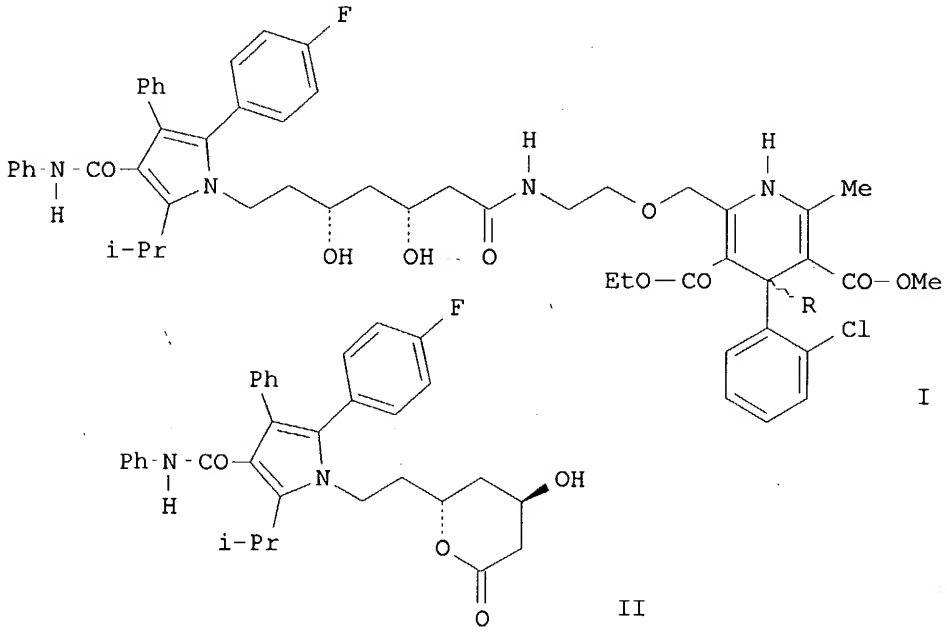

I

II

AB The present invention discloses the prepn. of an amide-linked amlodipine/atorvastatin prodrug I and pharmaceutically acceptable acid addn. salts [wherein: R = H with (R), (S), or (R/S) stereochem.]. For example, a soln. of **R**(-)-**amlodipine** (2 mmol) and atorvastatin lactone II (1.8 mmol) in ethanol (30 mL) was refluxed for 18 h. The solvent was then evapd. in vacuo and the resulting oil purified by column chromatog. to provide the prodrug I [R = (R)-H] as a white foam in 76% yield. Hydrolytic cleavage of the prodrug amide bond provides amlodipine and atorvastatin in vivo. Methods for clin. study of I in the treatment of atherosclerosis, angina pectoris, hypertension, hyperlipidemia and management of cardiac risk are described (no data).
NO HIGHLIGHTING INFORMATION PRESENT
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file caplus
FILE 'CAPLUS' ENTERED AT 14:28:48 ON 16 SEP 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

FILE COVERS 1907 - 16 Sep 2004 VOL 141 ISS 12
FILE LAST UPDATED: 15 Sep 2004 (20040915/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d que
L1 3 SEA FILE=CASREACT S(W)AMLODIPINE OR R(W)AMLODIPINE
L2 3 SEA FILE=CAPLUS L1

=> d l2 1-3 ibib abs hit

L2 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:252484 CAPLUS
DOCUMENT NUMBER: **140:287273**
TITLE: A process for the preparation of (S)-(-)-amlodipine nicotinate and its hydrates as antihypertensive agents with improved activity and photostability
INVENTOR(S): Chung, You-Sup; Ha, Mun-Choun
PATENT ASSIGNEE(S): Hanlim Pharmaceutical Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024690	A1	20040325	WO 2003-KR1850	20030908

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: KR 2002-54809 A 20020911
KR 2003-1260 A 20030109
OTHER SOURCE(S): CASREACT 140:287273
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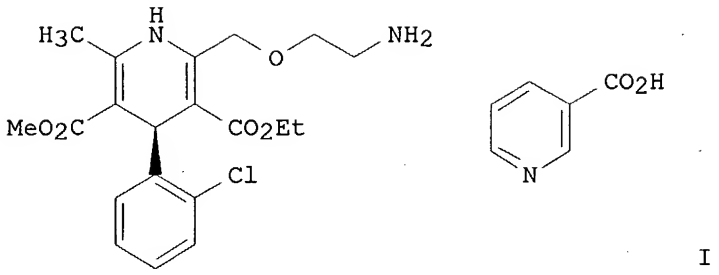

I

AB The dihydrate of (S)-(-)-amlodipine nicotinate I is prepd. as a form of (S)-(-)-amlodipine with improved antihypertensive activity and improved photostability. (S)-(-)-amlodipine in 95% methylated spirit is added to a slurry of nicotinic acid in 95% methylated spirit, slowly heated to reflux and stirred for five hours, and cooled to 5.degree. to form crystals which are washed with isopropanol; dissoln. of the salt in a 95:5 mixt. by mass (90:10 mixt. by vol.) of isopropanol and methanol, stirred at room temp. and slowly cooled to 0.degree. to yield the dihydrate of I as a ppt. I.bul.2H2O is found to be stable for three weeks under a 100 W incandescent bulb 30 cm. away, while (S)-(-)-amlodipine besylate absorbs water and changes color under the same conditions. I is slightly more active as an antihypertensive agent than racemic amlodipine nicotinate. The anhyd. and unspecified hydrate forms of I are also claimed. I and its hydrated forms are claimed as antiischemic and antihypertensive agents.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 2004:252484 CAPLUS
DN **140:287273**

L2 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:252483 CAPLUS
DOCUMENT NUMBER: **140:287272**
TITLE: Process for the preparation of (S)-(-)-amlodipine by resolution of (RS)-amlodipine with L-tartaric acid
INVENTOR(S): Chung, You-Sup; Ha, Mun-Choun
PATENT ASSIGNEE(S): Hanlim Pharmaceutical Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024689	A1	20040325	WO 2003-KR1849	20030908

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ,

GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: KR 2002-54808 A 20020911
OTHER SOURCE(S): CASREACT 140:287272
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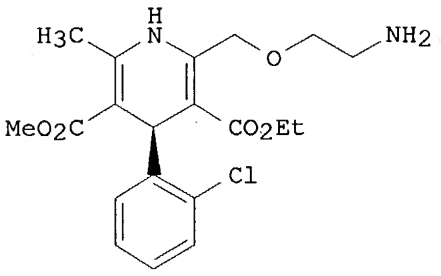

I

AB (S)-(-)-amlodipine I is prepd. from racemic amlodipine by a resoln. using L-(+)-tartaric acid; L-tartaric acid is much less expensive than the D-tartaric acid used in a previous method for the prepn. of I, decreasing the cost of resoln. and making resoln. of I more amenable to industrial scale synthesis. 0.5-0.55 Equiv. of L-(+)-tartaric acid in DMSO is added to racemic I in DMSO and stirred overnight at room temp. to yield a slurry from which the ppt. is filtered; addn. of methylene chloride to the filtered soln., stirring at ambient temp. for 40 h, cooling to 5.degree. and stirring for two hours yields a ppt. of the DMSO solvate of the L-hemitartrate salt of I. The amt. of DMSO present in the resoln. step should be between four to six times (preferably five times) the vol. of one gram of racemic amlodipine per g of amlodipine resolved, and the amt. of methylene chloride added afterwards should be one to two times the amt. of DMSO present. The DMSO solvate of the L-hemitartrate salt of I can be converted to the hydrate of the L-hemitartrate salt of I by refluxing in methanol to dissolve the DMSO solvate followed by overnight stirring and filtration. Treatment of a methylene chloride soln. of either the DMSO solvate of the L-hemitartrate salt of I or the hydrate of the L-hemitartrate salt of I with a 2 M soln. of sodium bicarbonate in water followed by cooling to 5.degree. and filtration yields I. I is prepd. on gram scale by this method.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 2004:252483 CAPLUS
DN **140:287272**

L2 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:364016 CAPLUS
DOCUMENT NUMBER: **136:369612**
TITLE: Preparation of an amlodipine/atorvastatin amide prodrug for the treatment of atherosclerosis, angina pectoris, hypertension, hyperlipidemia and management of cardiac risk.
INVENTOR(S): Crook, Robert J.; Pettman, Alan J.
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
EP 1205477	A1	20020515	EP 2001-309169		20011030
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
US 2002082282	A1	20020627	US 2001-985		20011031
US 6737430	B2	20040518			
BR 2001005080	A	20020625	BR 2001-5080		20011108
JP 2002179675	A2	20020626	JP 2001-344576		20011109
PRIORITY APPLN. INFO.:			GB 2000-27410	A	20001109
			US 2000-255025P	P	20001212

OTHER SOURCE(S): CASREACT 136:369612

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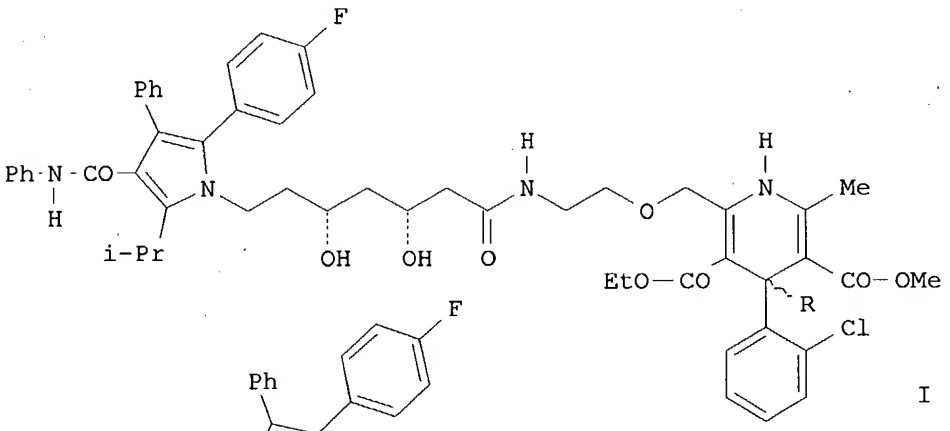

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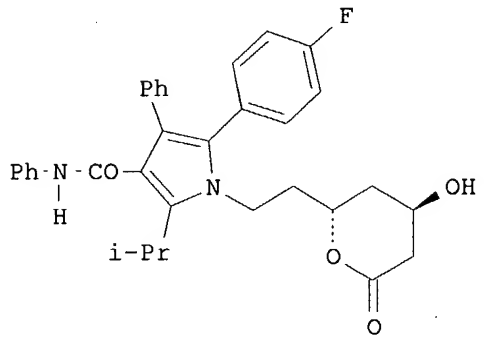

II

AB The present invention discloses the prepn. of an amide-linked amlodipine/atorvastatin prodrug I and pharmaceutically acceptable acid addn. salts [wherein: R = H with (R), (S), or (R/S) stereochem.]. For example, a soln. of R(-)-amlodipine (2 mmol) and atorvastatin lactone II (1.8 mmol) in ethanol (30 mL) was refluxed for 18 h. The solvent was then evapd. in vacuo and the resulting oil purified by column chromatog. to provide the prodrug I [R = (R)-H] as a white foam in 76% yield. Hydrolytic cleavage of the prodrug amide bond provides amlodipine and atorvastatin in vivo. Methods for clin. study of I in the treatment of atherosclerosis, angina pectoris, hypertension, hyperlipidemia and management of cardiac risk are described (no data).

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 2002:364016 CAPLUS

DN **136:369612**

=> file uspatall

FILE 'USPATFULL' ENTERED AT 14:29:41 ON 16 SEP 2004

FILE 'USPAT2' ENTERED AT 14:29:41 ON 16 SEP 2004

=> d que
L1 3 SEA FILE=CASREACT S(W)AMLODIPINE OR R(W)AMLODIPINE
L3 28 SEA L1

=> d l3 1-28 ibib abs hit

L3 ANSWER 1 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2004:204183 USPATFULL
TITLE: ORGANIC ACID SALT OF AMLODIPINE
INVENTOR(S): Youn, Yong Sik, Yongin-si, KOREA, REPUBLIC OF
Cho, Seong Hwan, Suwon-si, KOREA, REPUBLIC OF
Park, Choong Sil, Icheon-si, KOREA, REPUBLIC OF
Kim, Yun Cheul, Seoul, KOREA, REPUBLIC OF
Lim, Dong Kwon, Seongnam-si, KOREA, REPUBLIC OF
Jung, Sung Hak, Seoul, KOREA, REPUBLIC OF
Lee, Sung Hak, Yongin-si, KOREA, REPUBLIC OF
Kang, Hyun Suk, Seoul, KOREA, REPUBLIC OF
Park, Kyung Mi, Seoul, KOREA, REPUBLIC OF
Jung, Yun Taek, Seoul, KOREA, REPUBLIC OF
Kim, Young Hoon, Seoul, KOREA, REPUBLIC OF
Yeon, Kyu Jeong, Yongin-si, KOREA, REPUBLIC OF
Chae, Myeong Yun, Seongnam-si, KOREA, REPUBLIC OF
Jin, Hae Tak, Yongin-si, KOREA, REPUBLIC OF
Suh, Hea Ran, Ichon-si, KOREA, REPUBLIC OF
Lee, Kwang Hyeg, Seongnam-si, KOREA, REPUBLIC OF
Lee, Hyuk Koo, Yongin-si, KOREA, REPUBLIC OF
PATENT ASSIGNEE(S): CJ Corporation, Seoul, KOREA, REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004158075	A1	20040812	
APPLICATION INFO.:	US 2003-642754	A1	20030819	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	KR	20020821

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GREENBLUM & BERNSTEIN, P.L.C., 1950 ROLAND CLARKE PLACE, RESTON, VA, 20191
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
LINE COUNT: 427
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are a novel organic acid salt of amlodipine, its preparation method, and a pharmaceutical composition containing the same as a therapeutically active ingredient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0006] U. S. Pat. No. 6,291,490 introduces a pharmaceutical composition containing as an active ingredient **S**-(-)-**amlodipine** which possesses potent activity in treating hypertension without the adverse effects associated with the administration of the racemic mixture of amlodipine.

L3 ANSWER 2 OF 28 USPATFULL on STN

ACCESSION NUMBER:	2004:152256 USPATFULL
TITLE:	Novel amlodipine camsylate and method for preparing thereof
INVENTOR(S):	Moon, Young-Ho, Kyungki-do, KOREA, REPUBLIC OF Kim, Nam-Du, Kyungki-do, KOREA, REPUBLIC OF Lee, Kyung-Ik, Incheon, KOREA, REPUBLIC OF Lee, Gwan-Sun, Seoul, KOREA, REPUBLIC OF Woo, Jong-Soo, Kyungki-do, KOREA, REPUBLIC OF

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004116478	A1	20040617	
APPLICATION INFO.:	US 2003-473479	A1	20030926	(10)
	WO 2002-KR543		20020328	

	NUMBER	DATE
PRIORITY INFORMATION:	KR 2001-16514	20010329

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	David A Einhorn, Anderson Kill & Olick, 1251 Avenue of the Americas, New York, NY, 10020
NUMBER OF CLAIMS:	8
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	3 Drawing Page(s)
LINE COUNT:	348

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Amlodipine camsylate of the present invention is a crystalline salt of amlodipine suitable for pharmaceutical formulation, which is prepared by using low toxic camphor sulfonic acid to meet required pharmaceutical properties for treating cadiovacular diseases.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0047] An amlodipine salt preferably has a solubility in water of more 1 mg/ml at pH 1 to 7.5, particularly at the blood pH value of 7.4. Accordingly, the solubility and saturation pH of each of the amlodipine camsylates prepared in Examples 1 and 2 were measured and compared with those of amlodipine besylate (Korean Patent Publication No. 95-7228). The measurement was performed according to the procedure described in the Korean Pharmacopoeia (Korean Ministry of Health and Welfare, General principle of medical supplies, Vol. 1, Clause 29, the 7.sup.th revision) which comprises the steps of dissolving each compound in distilled water to saturation, analyzing the saturated solution with liquid chromatography, and measuring the dissolved amount of each compound based on the amount of amlodipine.

TABLE 2

Salt	Solubility (mg/ml)	Saturation pH
Amlodipine besylate	1.398	6.2
Amlodipine camsylate of Example 1 (**S**)	1.225	6.0
Amlodipine camsylate of Example 2 (R)	1.250	6.2

DETD [0049] The time-dependent stability of the inventive amlodipine camsylate prepared in Examples 1 and 2 was measured and compared with that of amlodipine besylate. Specifically, each compound was stored at 55.degree. C., a relative humidity of about 50%, and after 1, 2, 3 and 4 weeks, the remaining amount of active amlodipine was determined with a

liquid chromatography.

TABLE 3

Salt	Initial	1 week	2 weeks	3 weeks	4 weeks
Amlodipine besylate	1	0.992	0.996	0.993	0.993
Amlodipine camsylate of Example 1 (S)	1	1	0.998	1	1
Amlodipine camsylate of Example 2 (R)	1	1	1	1.002	1

DETD [0052] Each compound was exposed to two conditions: 37.degree. C. under 75% relative humidity for 24 hours (condition 1) and 30.degree. C. under 95% relative humidity for 3 days (condition 2), and then, the moisture content of each compound was measured according to the method described in Korean Patent Publication No. 1995-7228.

TABLE 4

Salt	Initial moisture (%)	Condition 1 (%)	Condition 2 (%)
Amlodipine besylate	0.05	0.05	0.15
Amlodipine camsylate of Example 1 (S)	0.05	0.05	0.15
Amlodipine camsylate of Example 2 (R)	0.05	0.05	0.15

L3 ANSWER 3 OF 28 USPATFULL on STN

ACCESSION NUMBER: 2004:95424 USPATFULL

TITLE: Crystalline 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-3-ethoxycarbonyl-5-methoxycarbonyl-6-methyl-1,4-dihydropyridine maleate salt (Amlodipine)

INVENTOR(S): Eswaraiah, Sajja, Hyderabad, INDIA
Reddy, Ganta Madhusudan, Hyderabad, INDIA
Reddy, Jambula Mukunda, Hyderabad, IN, UNITED STATES
Rambabu, Kammili Venkata, Hyderabad, INDIA
Bhaskar, Bolugoddu Vijaya, Hyderabad, INDIA

PATENT ASSIGNEE(S): DR. REDDY'S LABORATORIES LIMITED (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004072879	A1	20040415	
APPLICATION INFO.:	US 2002-269095	A1	20021010	(10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LADAS & PARRY, 26 WEST 61ST STREET, NEW YORK, NY, 10023
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 527
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel crystalline forms of Amlodipine Maleate These crystalline forms are useful as pharmaceutical agents.

This invention also relates to pharmaceutical compositions which include these crystalline forms and to methods of treatment using these crystalline forms. The novel crystalline compounds of the present invention are useful as calcium channel blockers and are thus useful as anti-ischaemic and anti-hypertensive agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0004] Use of Amlodipine in the therapy of cardiovascular disorders is known. Patent specification AU1354000 discloses a method for treating hypertension, angina and other disorders using optically pure (-) Amlodipine. U.S. Pat. No. 6,080,761 discloses the inhibition of smooth muscle migration by (**R**) **Amlodipine**. Flynn J T et al. describes the Treatment of hypertensive children with Amlodipine in Am. J. Hypertens., (AJHYE6, 08957061); 2000; Vol. 13 (10); pp. 1061-1066. Marche P discloses Amlodipine and the mechanisms of vascular hypertrophy in Drugs (DRUGAY, 00126667); 2000; Vol.59 (Spec. Issue 2); pp. 1-7. Burges R A explains the Pharmacologic profile of Amlodipine Am. J. Cardiol. (AJCDAG, 00029149); 1989; Vol.64 (17); pp. 101-201.

L3 ANSWER 4 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2004:95236 USPATFULL
TITLE: Novel propionic acid derivatives
INVENTOR(S): Kawanishi, Masashi, Tagata-gun, JAPAN
Umeno, Hiroshi, Tagata-gun, JAPAN

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004072690	A1	20040415
APPLICATION INFO.:	US 2003-367857	A1	20031010 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2002-45287	20020221
	US 2002-358328P	20020222 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
LINE COUNT: 15430
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound represented by the following formula (1) or a salt thereof:
##STR1##

wherein R.sup.1 represents a C.sub.1-12 alkyl group, phenyl group, 1-naphthyl group and the like, R.sup.2 represents a C.sub.2-12 alkyl group, (R.sup.3).sub.b represents 0 to 4 substituents such as a halogen atom, R.sup.4 represents a lower alkyl group, R.sup.5 represents hydrogen atom or a lower alkyl group, n represents an integer from 2 to 4, and X represents --NH-- or --O--, which has superior hypoglycemic action, hypolipidemic action and total cholesterol reducing action, and is useful as an active ingredient of a medicament for prophylactic and/or therapeutic treatment of diseases including diabetes mellitus, hyperlipidemia and the like.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [2043] 3-(4-{2-[1-(4-cyclohexylbutyl)-3-(3-methylphenyl)ureido]ethoxy}phenyl)-2-ethoxypropionic acid,

L3 ANSWER 5 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2004:77188 USPATFULL
TITLE: Crystalline organic acid salt of amlodipine
INVENTOR(S): Lim, Dong Kwon, Seongnam-city, KOREA, REPUBLIC OF
Lee, Hyuk Koo, Yongin-city, KOREA, REPUBLIC OF
Suh, Hea Ran, Icheon-city, KOREA, REPUBLIC OF
Cho, Seong Hwan, Suwon-city, KOREA, REPUBLIC OF
Lee, Kwang Hyeg, Seongnam-city, KOREA, REPUBLIC OF
Kim, Yun Cheul, Seoul, KOREA, REPUBLIC OF
Jung, Sung Hak, Seoul, KOREA, REPUBLIC OF
Lee, Sung Hak, Yongin-city, KOREA, REPUBLIC OF
Kang, Hyun Suk, Seoul, KOREA, REPUBLIC OF
Park, Kyung Mi, Seoul, KOREA, REPUBLIC OF
Jung, Yun Taek, Seoul, KOREA, REPUBLIC OF
Cheon, Jun Hee, Suwon-city, KOREA, REPUBLIC OF
Park, Choong Sil, Icheon-city, KOREA, REPUBLIC OF
Youn, Yong Sik, Yongin-city, KOREA, REPUBLIC OF
Kim, Young Hoon, Seoul, KOREA, REPUBLIC OF
Yeon, Kyu Jeong, Yongin-city, KOREA, REPUBLIC OF
Chae, Myeong Yun, Seongnam-city, KOREA, REPUBLIC OF
Jin, Hae Tak, Yongin-city, KOREA, REPUBLIC OF

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004058967	A1	20040325	
APPLICATION INFO.:	US 2003-652417	A1	20030829	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	KR 2002-57328	20020919
	KR 2003-53072	20030731

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CANTOR COLBURN, LLP, 55 GRIFFIN ROAD SOUTH, BLOOMFIELD, CT, 06002
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 463
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel crystalline organic acid salt of amlodipine having improved physiochemical properties, a preparation method thereof and a pharmaceutical composition comprising the same are provided.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0004] Amlodipine having a calcium channel blocking activity is useful in treating hypertension. As disclosed in EP 089 167, amlodipine is used in the form of salts formed with acids capable of forming non-toxic acid addition salts containing pharmaceutically acceptable anions, for example, hydrochloride, hydrobromide, sulphate, phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate salts. U.S. Pat. No. 6,291,490 discloses **S**-(-)-**amlodipine** that avoids the concomitant liability of adverse effects associated with the racemic mixture of amlodipine.

L3 ANSWER 6 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2004:39601 USPATFULL
TITLE: Organic acid salt of amlodipine
INVENTOR(S): Cho, Seong Hwan, Suwon-si, KOREA, REPUBLIC OF

Youn, Yong Sik, Yongin-si, KOREA, REPUBLIC OF
Jung, Yun Taek, Seoul, KOREA, REPUBLIC OF
Park, Choong Sil, Icheon-si, KOREA, REPUBLIC OF
Lee, Hyuk Koo, Yongin-si, KOREA, REPUBLIC OF
Lee, Kwang Hyeg, Seongnam-si, KOREA, REPUBLIC OF
Jeong, Eun Ju, Jincheon-gun, KOREA, REPUBLIC OF
Kim, Young Hoon, Seoul, KOREA, REPUBLIC OF
Jin, Hae Tak, Yongin-si, KOREA, REPUBLIC OF
Cheon, Jun Hee, Suwon-si, KOREA, REPUBLIC OF
Lee, Sung Hak, Yongin-si, KOREA, REPUBLIC OF
Jung, Sung Hak, Seoul, KOREA, REPUBLIC OF
Lim, Dong Kwon, Seongnam-si, KOREA, REPUBLIC OF
Yeon, Kyu Jeong, Yongin-si, KOREA, REPUBLIC OF
Kim, Yun Cheul, Seoul, KOREA, REPUBLIC OF
Park, Kyung Mi, Seoul, KOREA, REPUBLIC OF
Kang, Hyun Suk, Seoul, KOREA, REPUBLIC OF
PATENT ASSIGNEE(S): CJ Corp, Seoul, KOREA, REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004030143	A1	20040212	
APPLICATION INFO.:	US 2003-628209	A1	20030729	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	KR	20020730

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GREENBLUM & BERNSTEIN, P.L.C., 1950 ROLAND CLARKE PLACE, RESTON, VA, 20191
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 395
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are a novel organic acid salt of amlodipine, its preparation method, and a pharmaceutical composition containing the same as a therapeutically active ingredient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0006] U.S. Pat. No. 6,291,490 introduces a pharmaceutical composition containing as an active ingredient **S**-(-)-**amlodipine** which possesses potent activity in treating both systolic and diastolic hypertension while avoiding adverse effects associated with administration of the racemic mixture of amlodipine.

L3 ANSWER 7 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2004:39389 USPATFULL
TITLE: Organic acid salt of amlodipine
INVENTOR(S): Cho, Seong Hwan, Suwon-si, KOREA, REPUBLIC OF
Youn, Yong Sik, Yongin-si, KOREA, REPUBLIC OF
Jung, Yun Taek, Seoul, KOREA, REPUBLIC OF
Park, Choong Sil, Icheon-si, KOREA, REPUBLIC OF
Lee, Hyuk Koo, Yongin-si, KOREA, REPUBLIC OF
Lee, Kwang Hyeg, Seongnam-si, KOREA, REPUBLIC OF
Jeong, Eun Ju, Jincheon-gun, KOREA, REPUBLIC OF
Kim, Young Hoon, Seoul, KOREA, REPUBLIC OF
Jin, Hae Tak, Yongin-si, KOREA, REPUBLIC OF
Cheon, Jun Hee, Suwon-si, KOREA, REPUBLIC OF
Lee, Sung Hak, Yongin-si, KOREA, REPUBLIC OF

Jung, Sung Hak, Seoul, KOREA, REPUBLIC OF
Lim, Dong Kwon, Seongnam-si, KOREA, REPUBLIC OF
Yeon, Kyu Jeong, Yongin-si, KOREA, REPUBLIC OF
Kim, Yun Cheul, Seoul, KOREA, REPUBLIC OF
Park, Kyung Mi, Seoul, KOREA, REPUBLIC OF
Kang, Hyun Suk, Seoul, KOREA, REPUBLIC OF
PATENT ASSIGNEE(S): CJ Corp, Seoul, KOREA, REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004029931	A1	20040212	
APPLICATION INFO.:	US 2003-628268	A1	20030729	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	KR	20020730

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GREENBLUM & BERNSTEIN, P.L.C., 1950 ROLAND CLARKE PLACE, RESTON, VA, 20191
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 354
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are a novel organic acid salt of amlodipine, its preparation method, and a pharmaceutical composition containing as a therapeutically active ingredient the same.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0005] U.S. Pat. No. 6,291,490 introduces a pharmaceutical composition containing as an active ingredient **S**-(-)-**amlodipine** which possesses potent activity in treating hypertension without adverse effects associated with the administration of the racemic mixture of amlodipine.

L3 ANSWER 8 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2004:39381 USPATFULL
TITLE: Organic acid salt of amlodipine
INVENTOR(S): Cho, Seong Hwan, Suwon-si, KOREA, REPUBLIC OF
Youn, Yong Sik, Yongin-si, KOREA, REPUBLIC OF
Jung, Yun Taek, Seoul, KOREA, REPUBLIC OF
Park, Choong Sil, Icheon-si, KOREA, REPUBLIC OF
Lee, Hyuk Koo, Yongin-si, KOREA, REPUBLIC OF
Lee, Kwang Hyeg, Seongnam-si, KOREA, REPUBLIC OF
Jeong, Eun Ju, Jincheon-gun, KOREA, REPUBLIC OF
Kim, Young Hoon, Seoul, KOREA, REPUBLIC OF
Jin, Hae Tak, Yongin-si, KOREA, REPUBLIC OF
Cheon, Jun Hee, Suwon-si, KOREA, REPUBLIC OF
Lee, Sung Hak, Yongin-si, KOREA, REPUBLIC OF
Jung, Sung Hak, Seoul, KOREA, REPUBLIC OF
Lim, Dong Kwon, Seongnam-si, KOREA, REPUBLIC OF
Yeon, Kyu Jeong, Yongin-si, KOREA, REPUBLIC OF
Kim, Yun Cheul, Seoul, KOREA, REPUBLIC OF
Park, Kyung Mi, Seoul, KOREA, REPUBLIC OF
Kang, Hyun Suk, Seoul, KOREA, REPUBLIC OF
PATENT ASSIGNEE(S): CJ Corporation, Seoul, KOREA, REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE

PATENT INFORMATION:	US 2004029923	A1	20040212
	US 6756390	B2	20040629
APPLICATION INFO.:	US 2003-628210	A1	20030729 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	KR	20020730

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GREENBLUM & BERNSTEIN, P.L.C., 1950 ROLAND CLARKE PLACE, RESTON, VA, 20191
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
LINE COUNT: 463
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed are a novel organic acid salt of amlodipine with superb physicochemical properties, its preparation method, and a pharmaceutical composition containing the same as a therapeutically active ingredient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0006] U.S. Pat. No. 6,291,490 introduces a pharmaceutical composition containing as an active ingredient **S**-(-)-**amlodipine** which possesses potent activity in treating both systolic and diastolic hypertension while avoiding adverse effects associated with administration of the racemic mixture of amlodipine.

L3 ANSWER 9 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2004:1867 USPATFULL
TITLE: Stabilized pharmaceutical formulations containing amlodipine maleate
INVENTOR(S): Chakole, Dinesh Dayaramji, Hyderabad, INDIA
Reddy, Pallempalli Venkata Siva, Hyderabad, INDIA
Reddy, Billa Praveen, Hyderabad, INDIA
Dhanorkar, Vipin Tatyasaheb, Hyderabad, INDIA
Mohan, Mailatur Sivaraman, Hyderabad, INDIA
PATENT ASSIGNEE(S): DR. REDDY'S LABORATORIES LIMITED (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004001886	A1	20040101
APPLICATION INFO.:	US 2003-417810	A1	20030417 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-244049, filed on 13 Sep 2002, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	IN 2001-8522001	20011017
	WO 2002-US22908	20020718

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LADAS & PARRY, 26 WEST 61ST STREET, NEW YORK, NY, 10023
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
LINE COUNT: 778
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the stable solid orally administrable pharmaceutical formulation of Amlodipine Maleate. The invention also describes the process of producing such stable formulations and more specifically a direct compression method of producing tablet

formulations. The tablet formulation of Amlodipine Maleate thus prepared is bioequivalent to the tablets containing Amlodipine Besylate salt commercially available with the brand name of Norvasc. The formulation also avoids the common problem of sticking observed during manufacturing.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0004] Use of Amlodipine in the therapy of cardiovascular disorders is known. Patent specification AU1354000 discloses a method for treating hypertension, angina and other disorders using optically pure (-) Amlodipine. U.S. Pat. No. 6,080,761 discloses the inhibition of smooth muscle migration by (R) **Amlodipine**. Flynn J T et al. describes the Treatment of hypertensive children with Amlodipine in Am. J. Hypertens. (AJHYE6, 08957061); 2000; Vol. 13 (10); pp. 1061-1066. Marche P discloses Amlodipine and the mechanisms of vascular hypertrophy in Drugs (DRUGAY, 00126667); 2000; Vol.59 (Spec. Issue 2); pp.1-7. Burges R A explains the Pharmacologic profile of Amlodipine Am. J. Cardiol. (AJCDAG, 00029149); 1989; Vol.64 (17); pp.10I-20I.

L3 ANSWER 10 OF 28 USPATFULL on STN

ACCESSION NUMBER: 2003:257304 USPATFULL

TITLE: Amlodipine maleate formulations

INVENTOR(S): Chakole, Dinesh Dayaramji, Hyderabad, INDIA
Reddy, Pallempalli Venkata Siva, Hyderabad, INDIA
Reddy, Billa Praveen, Hyderabad, INDIA
Dhanorkar, Vipin Tatyasaheb, Hyderabad, INDIA
Mohan, Mailatur Sivaraman, Hyderabad, INDIA

PATENT ASSIGNEE(S): DR. REDDY'S LABORATORIES LIMITED (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003180354	A1	20030925	
APPLICATION INFO.:	US 2002-244048	A1	20020913	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	IN 2001-8522001	20011017
	WO 2002-US22908	20020718

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Ladas & Parry, 26 West 61 Street, New York, NY, 10023

NUMBER OF CLAIMS: 24

EXEMPLARY CLAIM: 1

LINE COUNT: 764

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to the stable solid orally administrable pharmaceutical formulation of Amlodipine Maleate. The invention also describes the process of producing such stable formulations and more specifically a direct compression method of producing tablet formulations. The tablet formulation of Amlodipine Maleate thus prepared is bioequivalent to the tablets containing Amlodipine Besylate salt commercially available with the brand name of Norvasc. The formulation also avoids the common problem of sticking observed during manufacturing.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0004] Use of Amlodipine in the therapy of cardiovascular disorders is known. Patent specification AU1354000 discloses a method for treating hypertension, angina and other disorders using optically pure (-) Amlodipine. U.S. Pat. No. 6,080,761 discloses the inhibition of smooth

muscle migration by (**R**) **Amlodipine**. Flynn J T et al. describes the Treatment of hypertensive children with Amlodipine in Am. J. Hypertens. (AJHYE6, 08957061); 2000; Vol. 13 (10); pp. 1061-1066. Marche P discloses Amlodipine and the mechanisms of vascular hypertrophy in Drugs (DRUGAY, 00126667); 2000; Vol.59 (Spec. Issue 2); pp.1-7. Burges R A explains the Pharmacologic profile of Amlodipine Am. J. Cardiol. (AJCDAG, 00029149); 1989; Vol.64 (17); pp.101-201.

L3 ANSWER 11 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2003:251917 USPATFULL
TITLE: Process for the preparation of [**S**(-) **amlodipine** - L (+)- hemitartarate]
INVENTOR(S): Joshi, Rohini Ramesh, Maharashtra, INDIA
Joshi, Ramesh Anna, Maharashtra, INDIA
Gurjab, M. K, Pune, INDIA

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003176706	A1	20030918	
APPLICATION INFO.:	US 2002-98502	A1	20020318	(10)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Norman H. Stepno, Esquire, BURNS, DOANE, SWECKER & MATHIS, L.L.P., P.O. Box 1404, Alexandria, VA, 22313-1404
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
LINE COUNT: 157
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a process for the preparation of [**S**(-)**amlodipine**-L(+)-hemi taratarte] from RS amlodipine base using L(+) tartaric acid in the presence of dimethyl sulfoxide.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Process for the preparation of [**S**(-) **amlodipine** - L (+)- hemitartarate]
AB The present invention relates to a process for the preparation of [**S**(-)**amlodipine**-L(+)-hemi taratarte] from RS amlodipine base using L(+) tartaric acid in the presence of dimethyl sulfoxide.
SUMM [0001] The present invention relates to a process for the preparation of [**S**(-)**amlodipine**-L(+)-hemi taratarte] from RS amlodipine base using L(+) tartaric acid in the presence of dimethyl sulfoxide.

SUMM [0006] 1. The use of unnatural tartaric acid for the separation of **S**(-)**amlodipine**

SUMM [0008] The main object of the invention is to develop a technology for the preparation of **S**(-)**amlodipine** from racemic amlodipine using naturally occurring L-tataric acid.

SUMM [0009] Accordingly, the invention provides a new and efficient process for the preparation of [**S**(-)**amlodipine**-L(+)hemi tartarte] in good yield with high enantiomeric purity by reacting RS amlodipine base with L(+) tartaric acid in an organic solvent at a temperature ranging from 20-35.degree. C. for a period ranging from 16 to 24 hours, separating by filtration solid [**R**(+) **amlodipine**-L(+)-hemi taratarte], seeding the filtrate to obtain solid [S(-) amlodipin-L(+)-hemi taratarte], filtering and recrystallising the solid, basifying to obtain **S**(-)

amlodipine.

DETD [0016] Amlodipine hemi L tartarate-mono-DMSO Solvate mp 160-162.degree. C. [.alpha.].sup.t=+24.32 (c=1, **R**(+) **Amlodipine** -hemi-L-tartarate mono DMSO Solvate and **S**(-) **Amlodipine**-hemi-L tartarate mono DMSO Solvate from (RS) Amlodipine.

DETD [0017] To a stirred solution of 10.50 gm (0.0256 mole), of RS Amlodipine in 30 ml of DMSO was added a solution of 1.93 (0.128) mole (0.5 equiv) of L(+) Tartaric acid in 30 ml DMSO. The solid starts separating from clear solution within 5-10 min. This was stirred for 3 hrs. and the solid was filtered off, washed with acetone and dried to give 6.66 gm, 46.15% R(+) MeOH). The filtrate was seeded with **S**(-) **amlodipine** hemi L(+) tartarate salt. and left overnight the solid was filtered off and washed with 10 ml acetone and dried to give 6.41 gm, 44.4% **S**(-) **amlodipine**-hemi L(+)-tartarate mono DMSO solvate.mp 169.5-171.5.degree. C.=-14.1 (c=1, MeOH) 90% de by chiral HPLC. (J.Chrom., B 693, 367 (1997) J. Luksa, Dj. Josic, B. Podobinc, B. Furlan, M. Kremser]

DETD [0020] **S**(-)**Amlodipine** hemi L(+)tartarate monohydrate from **S**(-) **Amlodipine**-hemi-L-(+)tartarate monohydrate DMSO Solvate--Methanol as Solvent.

DETD [0021] 50 gms of **S**(-) **Amlodipine**-hemi-L(+)-tartarate mohohydrate DMSO solvate was dissolved in 250 ml refluxing methanol (30 min). The solution was kept overnight at room temperature (25-28.degree. C.) with stirring. The solid was collected by filtration, washed with 100 ml methanol and dried at 50.degree. C. in vacuo (2 hrs till constant wt.) to give 35 gm (80%). **S**(-)**Amlodipine** -hemi-L(+)-tartarate monohydrate. Mp 171-172.degree. C.=114.1 (c=1, MeOH); 90% de chiral HPLC.

DETD [0022] **S**(-)**Amlodipine** hemi L(+)-tartarte mohohydrate from **S**(-) **Amlodipine**-hemi-L-(+)tartarate monohydrate DMSO Solvate--Ethanol as Solvent.

DETD [0023] The procedure was followed as mentioned in example 3 was using ethanol (150 ml) instead of methanol. The solid obtained was collected by filtration, washed with 50 ml cold ethanol and dried at 50.degree. C. in vacuo (2 hrs till constant wt.) to give 30 gms (68%). **S**(-) **Amlodipine** hemi L(+)tartarate monohydrate mp 172.5-174.degree. C.=17.44 (C=1, MeOH), 97% de chiral HPLC.

DETD [0024] **S**(-)**Amlodipine** from (**S**) (-) **Amlodipine** hemi L(+)tartarte mohonydrate.

DETD [0025] **S**(-)**Amlodipine** hemi L(+)tartarate mohohydrate (30 gms) was slurried in 60 ml CH.sub.2Cl.sub.2 and 60 ml (6%) aqueous ammonia for 30 min. The organic solution was separated and washed with water. The organic extract was dried to give solid. The solid was filtered and dried at room temperature under vacuo to give 20 gms (82%) **S**(-)**amlodipine** mp 108-109.degree. C. 30.55 (c=1, MeOH), 97.4% ee by chiral HPLC.

DETD [0026] **S**(-)**Amlodipine** from **S**(-) **Amlodipine** hemi L(+)tartarte mono DMSO Solvate

DETD [0027] **S**(-)**Amlodipine** hemi L(+)-tartarate mono DMSO solvate (30 gms) was slurried in 60 ml CH.sub.2Cl.sub.2 and 60 ml (6%) aqueous ammonia for 30 min. The organic solution was separated and washed with water. The organic extract was dried over anhydrous sodium sulphate and concentrated. The residue was triturated with hexane to give solid 20.1 gms (92%) **S**(-)**amlodipine**. Mp107-107.5.degree. C. 27.3 (c=1, MeOH), 90% ee by chiral HPLC.

CLM What is claimed is:

1. A process for the preparation of [**S**(-)**amlodipine** -L(+)-hemi tartarte which comprises reacting RS amlodipine base with L(+)tartaric acid in an organic solvent at a temperature ranging from

20-35.degree. C. for the period ranging from 16 to 24 hours, separating the solid [R(=)amlodipin-L(+)-hemi tartarate] by filtration, seeding the filtrate to obtain solid [S(-)amlodipin-L(+)-hemi tartarate] by precipitation, filtering the solid and basifying to obtain [**S**(-)**amlodipine**-L(+)-hemi tartarte.

6. A process claimed in claim 1 wherein a stirred solution of RS Amlodipine in DMSO was added to a solution of L(+)Tartaric acid in DMSO, the solid obtained separated by filtration, washed with acetone, dried to give R(+) MeOH), the filtrate seeded with **S**(-) **amlodipine** hemi L(+)tartarate salt, the solid so obtained filtered off and washed with acetone and dried to give **S**(-) **amlodipine**-hemi L(+)-tartarate mono DMSO solvate.

L3 ANSWER 12 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2003:222183 USPATFULL
TITLE: Process for making **S**(-) **Amlodipine** salts
INVENTOR(S): Joshi, Rohini Ramesh, Pune, INDIA
Joshi, Ramesh Anna, Pune, INDIA
Gurjar, Mukund Keshav, Pune, INDIA
PATENT ASSIGNEE(S): Council of Scientific & Industrial Research, New Delhi, INDIA (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6608206	B1	20030819	
APPLICATION INFO.:	US 2002-283762		20021030	(10)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Morris, Patricia L.
LEGAL REPRESENTATIVE: Luedeka, Neely & Graham PC
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 214
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A process for the preparation of **S**(-) **Amlodipine** salts which comprises reaction of **S**(-)**Amlodipine** base with a solution of pharmaceutically acceptable acid such as benzene sulfonic acid, oxalic acid, maleic acid, succinic acid and p-toluene sulfonic acid. The reaction is carried out in the presence of an organic solvent at room temperature. The organic solvents include alcohols like ethanol methanol 2 propanol hydrocarbons like toluene and polar solvent like dimethyl sulfoxide. The salt is obtained by addition of water and isolation of the salt formed by filtration. The unique feature of the invention is production of **S**(-) **Amlodipine** besylate in good chemical yield, high enantiomeric purity and with the quality required for preparation of pharmaceutical composition i.e. tablet formulation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Process for making **S**(-) **Amlodipine** salts
AB A process for the preparation of **S**(-) **Amlodipine** salts which comprises reaction of **S**(-)**Amlodipine** base with a solution of pharmaceutically acceptable acid such as benzene sulfonic acid, oxalic acid, maleic acid, succinic acid and p-toluene sulfonic acid. The reaction is carried out in the presence of an organic solvent at room temperature. The organic solvents include alcohols like ethanol methanol 2 propanol hydrocarbons like toluene and polar solvent

like dimethyl sulfoxide. The salt is obtained by addition of water and isolation of the salt formed by filtration. The unique feature of the invention is production of **S**(-) **Amlodipine** besylate in good chemical yield, high enantiomeric purity and with the quality required for preparation of pharmaceutical composition i.e. tablet formulation.

SUMM This invention relates to a process for the preparation of **S** (-) **Amlodipine** salts. More particularly it relates to the process for the preparation of pharmaceutically acceptable salts of **S**(-)**Amlodipine** such as besylate, succinate, maleate, oxalate and tosylate. The **S** (-) **Amlodipine** salts of general formula (1) ##STR1##

SUMM Salts of **S**(-) **Amlodipine** are prepared as per the procedure of the present invention from **S** (-) **Amlodipine**, the procedure for the preparation of the **S** (-) **Amlodipine** has been fully described and claimed in co-pending Indian patent application No. NF 383/2001.

SUMM Of all the salts of **S** (-) **Amlodipine** mentioned above, the compound **S** (-) **Amlodipine** besylate; (4-S)-2-{[(2-aminoethyl)oxy]methyl}-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzene sulfonate has commercial importance and is a potent and long acting calcium channel blocker.

SUMM (R,**S**)-**Amlodipine** besylate is currently being used for the treatment of cardiovascular disorders, in particular in the treatment of hypertension and angina, Amlodipine is a racemic compound and has chiral center at 4 position of dihydropyridine ring. The S(-) isomer has calcium channel blocker activity while the R(+)-isomer has little or no calcium channel blocking activity.

SUMM The compound R,**S**-**Amlodipine** is a potent and long acting calcium channel blocker having utility as an anti-ischaenic and anti-hypertensive agent. Although amlodipine is effective as the free base in practice it is best administered in the form of a salt of pharmaceutically acceptable acid, such as hydrochloride, hydrobromide, maleate, fumarate, tartarate and besylate.

SUMM Preparation of R and **S amlodipine** maleate salt has been reported starting from azido precursor. The procedure involves resolution of azido precursor using 2-methoxy-2-phenyl ethanol as a resolving agent, separation of diastereomer, ester exchange with sodium methoxide, hydrogenation, chromatographic purification and maleate salt formation. (J. Med. Chem., No. 29, p. 1896, (1986). J. E. Arrowsmith, S. F. Campbell, P. E. Cross, J. K. Stabs, R. A. Burges).

SUMM Preparation of preferred amlodipine besylate salt has been disclosed in the publication (J. Chrom.B 693 (1997) pp. 367-375, J. Luksa, Dj. Josic, B. Podobnik, B. Furlan, M. Kremser) describing the treatment of ethanolic solution of base with benzene sulfonic acid and isolation. The detailed procedures to obtain these salts have not been provided by the prior art. These prior art references also lack in providing physical or structural data given except the optical rotation except maleate. The main object of the present invention therefore to provide a process for the preparation of **S** (-) **Amlodipine** salts.

SUMM Accordingly the present invention provides a process for the preparation of **S**(-) **Amlodipine** salts of general formula (1) ##STR2##

SUMM Wherein R=Benzene sulfonic acid, succinic acid, maleic acid, oxalic acid and p-toluene sulfonic acid, which comprises reacting **S** (-) **amlodipine** base with a solution of an acid in presence of an organic solvent at room temperature, adding water to obtain the product in solid form.

SUMM The unique feature of the invention is production of **S** (-) **amlodipine** besylate with the quality required for preparation of pharmaceutical composition i.e. tablet formulation.

DETD Amlodipine maleate from **S** (-) **Amlodipine**

DETD **S** (-) **Amlodipine** (5.0 gms, 0.012 moles, 98.2 ee) was dissolved in ethanol(10 ml) and maleic acid (1.42 gms, 0.012 moles) in 70 ml of water was added with stirring. The separated solid was filtered washed with cold water, washed with hexane and dried under vacuo to give 5.32 gms (82.88%) of **S**(-) **amlodipine** maleate, mp. 176-177.degree. C. Optical rotation [.alpha.].sup.t.sub.D=-25.10 (c=1, MeOH) 98.3 1ee.

DETD Amlodipine oxalate from **S** (-) **Amlodipine**

DETD **S** (-) **Amlodipine** (5.0 gms, 0.012 moles, 98.2 ee) was dissolved in ethanol (10 ml) and oxalic acid (1.54 gms, 0.012 moles) in 70 ml of water was added with stirring. The separated solid was filtered washed with cold water, washed with hexane and dried under vacuo to give 5.80 gms (89.2%) of **S**(-) **amlodipine** oxalate. mp. 201-203.degree. C. Optical rotation [.alpha.].sup.t.sub.D=-27.95 (c=1, MeOH) 98.41ee.

DETD Amlodipine succinate from **S** (-) **Amlodipine**

DETD **S** (-) **Amlodipine** (5.0 gms, 0.012 moles, 98.2 ee) was dissolved in ethanol (10 ml) and succinic acid (1.44 gms 0.012 moles) in 70 ml of water was added with stirring. The separated solid was filtered washed with cold water, washed with hexane and dried under vacuo to give 6.0 gms (93.0%) of **S**(-) **amlodipine** succinate, mp. 169-171.degree. C. Optical rotation [.alpha.].sup.t.sub.D=-24.55 (c=1, MeOH) 97.95ee.

DETD Amlodipine tosylate from **S** (-) **Amlodipine**

DETD **S** (-) **Amlodipine** (5.0 gms, 0.012 moles, 98.2 ee) was dissolved in ethanol (10 ml) and p-toluene sulfonic acid (2.32gms, 0.012 moles) in 70 ml of water was added with stirring. The separated solid was filtered washed with cold water, washed with hexane and dried under vacuo to give 5.32 gms (82.88%) of **S**(-) **amlodipine** tosylate, mp. 114-117.degree. C. Optical rotation [.alpha.].sup.t.sub.D=-20.2 (c=1, MeOH) 98.23ee.

DETD Amlodipine besylate from **S** (-) **Amlodipine**

DETD **S** (-) **Amlodipine** (5.0 gms, 0.012 moles, 98.2 ee) was dissolved in ethanol (10 ml) and benzene sulfonic acid (1.93 gms, 0.012 moles) in 70 ml of water was added with stirring. The separated solid was filtered washed with cold water, washed with hexane and dried under vacuo to give 5.32 gms (82.88%) of **S**(-) **amlodipine** besylate, 10 mp. 67-68 softens 107-108.degree. C. Optical rotation [.alpha.].sup.t.sub.D=-21.50 (c=1, MeOH) 98.15ee. Microanalysis=C, 50.91%; H, 6.3%; N, 4.67%; S, 5.91%: Calc for C.sub.20H.sub.24O.sub.5N.sub.2Cl. C.sub.6H.sub.6O.sub.3S. 2.5 (H.sub.2O), C, 51.1%; H, 5.7%; N, 4.58%; S, 5.24%.

DETD a) **S**(-)**Amlodipine**-besylate from **S**(-)-**Amlodipine**

DETD **S**(-) **Amlodipine** (62 gms, 0.152 moles, 93.1 ee) was dissolved in isopropanol (62 ml) and a solution of benzene sulfonic acid (24 gm, 0.152 moles) in 50 ml water was added maintaining the temperature .about.20.degree. C. The reaction mixture was stirred for 30 min. and distilled water (450 ml) was added. The besylate salt separated after 20 min. stirring continued for one hr. and the slurry was

filtered. Washed with distilled water, hexane. The solid was dried under vac. at 40.degree. C. till constant wt. to give **S**(-) **Amlodipine** besylate (83 gm, 89% yield) 93.3 ee.

DETD b) Recrystallisation of **S**(-) **Amlodipine** besylate

DETD **S**(-) **Amlodipine** besylate (80 gms., 93.1 ee) was dissolved in isopropanol (80 ml) The reaction mixture was stirred for 30 min. and distilled water (640 ml) was added. The besylate salt separated after 20 min. stirring continued for one hr. and the slurry was filtered. Washed with distilled water, hexane. The solid was dried under vacuo at 40.degree. C. till constant wt. to give **S**(-) **Amlodipine** besylate (63 gm, 98.43 ee).

DETD **S**(-)**Amlodipine**-besylate from **S**(-)-**Amlodipine**

DETD **S**(-) **Amlodipine** (62 gms, 0.152 moles, 98.2 ee) was dissolved in isopropanol (62 ml) and a solution of benzene sulfonic acid (24 gm, 0.152 moles) in 50 ml water was added maintaining the temperature .about.20.degree. C. The reaction mixture was stirred for 30 min. and distilled water (450 ml) was added. The besylate salt separated after 20 min. stirring continued for one hr and the slurry was filtered. Washed with distilled water, hexane. The solid was dried under vacuo at 40.degree. C. till constant wt. to give **S**(-) **Amlodipine** besylate (83 gm, 89% yield) 98.3 ee.

DETD The process describes for the first time in detail the preparation of **S**(-)**Amlodipine** besylate salt in good chemical yields, high enantiomeric purity and with the quality required for preparation of pharmaceutical composition i.e. tablet formulation.

CLM What is claimed is:

1. A process for the preparation of **S**(-) **Amlodipine** salts of general formula (1) ##STR3## wherein R=Benzene sulfonic acid, succinic acid, maleic acid, oxalic acid and p-toluene sulfonic acid, which comprises reacting **S** (-) **amlodipine** base with a solution of an acid in presence of an organic solvent at room temperature, adding water to obtain the product in solid form.

L3 ANSWER 13 OF 28 USPATFULL on STN

ACCESSION NUMBER:	2003:188528 USPATFULL
TITLE:	Method of resolving amlodipine racemate
INVENTOR(S):	Senanayake, Chris H., Danbury, CT, UNITED STATES Tanoury, Gerald J., Hudson, MA, UNITED STATES Wilkinson, Harold S., Marlborough, MA, UNITED STATES Bakale, Roger P., Shrewsbury, MA, UNITED STATES Zlota, Andrei A., Sharon, MA, UNITED STATES
PATENT ASSIGNEE(S):	Sepracor, Inc., Marlborough, MA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003130321	A1	20030710
APPLICATION INFO.:	US 2002-325686	A1	20021220 (10)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 2002-US33894, filed on 23 Oct 2002, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-346250P	20011024 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	ROPES & GRAY LLP, ONE INTERNATIONAL PLACE, BOSTON, MA, 02110-2624
NUMBER OF CLAIMS:	29
EXEMPLARY CLAIM:	1

LINE COUNT: 491
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to methods of resolving racemic amlodipine into enantiomerically enriched compositions by precipitation with tartaric acid in the presence of a non-aqueous solvent, such as N,N'-dimethylacetamide. The molar ratio of tartaric acid:amlodipine is preferably less than 0.25:1.0 or greater than 0.75:1.0.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0004] The synthesis of racemic amlodipine (3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate) and its activity as an inhibitor of calcium channels is described in U.S. Pat. No. 4,572,909 to Campbell et al. Results of in vitro tests to determine calcium antagonist activity of amlodipine enantiomers against calcium-induced constriction of potassium-depolarized rat aorta is described in Arrowsmith et al., J. Med. Chem., (1986) 29, 1696-1702. The authors allege that the (-) stereoisomer is twice as active as the racemic mixture in antagonizing calcium-induced constriction. The S absolute configuration is the (-) optical rotatory form. Goldmann, J. Med. Chem., (1992)35, 3341-44. Desirability of optically pure **S**-(-)-**amlodipine** for treatment of hypertension and angina is described in U.S. Pat. No. 6,057,344.

SUMM [0005] Although **R**-(+)-**amlodipine** appears to have little activity as a calcium channel blocker, it is not pharmacologically inert, but rather it is a potent inhibitor of smooth muscle cell migration. WO 95/05822 (now U.S. Pat. No. 6,080,761) to Chahwala et al. Ideally, the preferred mode of using amlodipine would be the administration of the S-(-) enantiomer substantially free of the R-(+) enantiomer. U.S. Pat. No. 6,057,344 to Young. Nonetheless, there is presently no amlodipine product that contains **S**-(-)-**amlodipine** substantially free of the R-(+) enantiomer. See, for example, NORVASC.RTM., the active ingredient of which is racemic amlodipine besylate.

SUMM [0011] In another aspect, the invention is directed to a crystalline composition comprising **S**-(-)-**amlodipine** D-hemitartrate DMAC monosolvate or, alternatively, **R**-(+)-**amlodipine** L-hemitartrate DMAC monosolvate, wherein at least 80% of the amlodipine in the crystalline composition is the predominant enantiomer. Preferably at least 90% of the amlodipine in the crystalline composition is the predominant enantiomer. More preferably at least 97% of the amlodipine in the crystalline composition is the predominant enantiomer. Most preferably at least 99% of the amlodipine in the crystalline composition is the predominant enantiomer.

SUMM [0012] In yet another embodiment, the invention is directed to solid pharmaceutical dosage forms comprising an optically active amlodipine or a pharmaceutically acceptable salt or hydrate thereof, and a carrier matrix, and to methods for manufacturing such dosage forms. In certain preferred embodiments, at least 80% of the optically active amlodipine in the dosage form is **S**-(-)-**amlodipine**, preferably at least 90%, or even 95% or more.

SUMM [0019] In one embodiment, the amlodipine hemitartrate DMAC monosolvate precipitate can be formed as follows. The absolute concentrations in this embodiment are merely exemplary, and can be varied as determined by routine experimentation. Racemic amlodipine free base is dissolved in a solvent comprising DMAC. The solvent comprises sufficient DMAC to induce crystallization of the DMAC solvate of amlodipine, e.g., at least 50%

DMAC, preferably at least 80%, at least 90%, approximately 100% DMAC, or otherwise consisting essentially of DMAC, and may include amlodipine solute at a concentration of about 0.55 M, for example. If the starting material is an amlodipine acid addition salt, such as a besylate salt of amlodipine, the free base can be formed by any suitable technique as is well known in the art, such as extraction of an amlodipine salt suspension in MTBE (e.g., about 0.25 M) with aqueous NaOH, followed by concentration of the resultant free base by vacuum distillation. To the free base solution in the solvent, is added D- or L-tartaric acid. The tartaric acid may be added as a solid or, preferably, as a solution in either DMAC, the solvent used to dissolve the amlodipine, or any other suitable solvent, optionally at a concentration of about 0.55 M. D-Tartaric acid is used to precipitate **S**-(-)-**amlodipine** as the **S**-(-)-**amlodipine** D-hemitartrate DMAC monosolvate and L-tartaric acid precipitates **R**-(+)-**amlodipine** as the **R**-(+)-**amlodipine** L-hemitartrate DMAC monosolvate. The ratio of tartaric acid to racemic amlodipine is preferably less than about 0.3 mol tartaric acid per mol racemic amlodipine or greater than about 0.7 mol tartaric acid per mol racemic amlodipine.

DETD [0038] **S**-(-)-**amlodipine** D-hemitartrate DMAC Monosolvate

DETD [0039] Aqueous sodium hydroxide (1 N, 530 mL) was added to a stirred suspension of amlodipine besylate (200 g, 0.353 moles) in methyl t-butyl ether (1.3 L). The reaction mixture was stirred for 20-30 minutes after which the aqueous and organic layers were allowed to separate. After removing the aqueous layer, water (220 mL) was added to the organic layer and the mixture was stirred for 20 minutes. The aqueous layer was again removed and the organic layer was concentrated to approximately one-third of its original volume by vacuum distillation. The organic layer was collected and concentrated to approximately one-third of its original volume by distillation. The concentrate was then mixed with N,N-dimethylacetamide (DMAC, 650 ml) and further concentrated by vacuum distillation until the temperature of the concentrate rose by 10-15.degree. C. The concentrate was allowed to equilibrate to room temperature and pressure before it was added to a stirred solution of D-tartaric acid (55.12 g, 0.367 mol) in N,N-dimethylacetamide (650 mL). The resulting slurry was stirred for 3-5 hr followed by filtration. After the residual crystalline solid was washed successively with dimethylacetamide (650 mL) and methyl t-butyl ether (650 mL), it was dried in vacuo at 40-50.degree. C. for 8-16 hr to yield, **S**-(-)-**amlodipine** D-hemitartrate DMAC monosolvate (85.5 g, 41% yield, 98.98% enantiomeric purity, >99% chemical purity).

DETD [0040] **S**-(-)-**amlodipine** Free Base

DETD [0041] Aqueous sodium hydroxide (1 N, 220 mL) was added to a stirred suspension of **S**-(-)-**amlodipine** D-hemitartrate DMAC monosolvate (81.1 g, 0.142 moles) in methyl t-butyl ether (960 mL). The reaction mixture was stirred for 20-30 minutes after which the aqueous and organic layers were allowed to separate. After removing the aqueous layer, water (220 mL) was added to the organic layer and the mixture was stirred for 20 minutes. The aqueous layer was again removed and the organic layer was concentrated to approximately one-third of its original volume by vacuum distillation. After allowing the concentrate to equilibrate to room temperature and pressure, heptane (320 mL) was added and the resulting slurry was stirred for 1-2 hr. The slurry was then filtered, and the residual crystalline solid was washed with heptane (500 mL). The crystals were dried in vacuo at 40-50.degree. C. for 8-16 h to yield **S**-(-)-**amlodipine** free base (49.10 g, 85% yield, 99.96% enantiomeric purity, >99% chemical purity).

DETD [0042] **S**-(-)-**amlodipine** D-hemitartrate DMAC

Monosolvate

DETD [0043] (RS)-amlodipine (24.85 kg, 60.8 moles) and N,N-dimethylacetamide (DMAC, 104 kg) are added to a reactor and stirred at 20 to 25.degree. C. for 15 to 30 minutes. A solution of D-tartaric acid (9.5 kg, 63.2 mol) in N,N-dimethylacetamide (104 kg) is added at 20 to 25.degree. C. The mixture is heated to 68 to 70.degree. C. over about 60 minutes and stirred for about 60 minutes. The solution is cooled to 20 to 23.degree. C. over 2 to 3 hr and the slurry is then held for about 30 to 45 minutes at 20 to 23.degree. C. The slurry is then filtered and the residual crystalline solid is washed successively with N,N-dimethylacetamide (about 50 kg) and methyl t-butyl ether (about 40 kg). The filter cake is dried in vacuo at 40 to 50.degree. C. for 8 to 16 hr to yield, **S**-(-)-**amlodipine** D-hemitartrate DMAC monosolvate (14 kg, 40% yield, 99.2% enantiomeric purity, >99% chemical purity).

DETD [0044] **S**-(-)-**amlodipine** Free Base

DETD [0045] Aqueous sodium hydroxide (75.8 kg, 1 N) is added to a stirred suspension of **S**-(-)-**amlodipine** D-hemitartrate DMAC monosolvate (26.9 kg, 47.4 moles) in methyl t-butyl ether (220 kg). The reaction mixture is stirred for 20 to 30 minutes after which the aqueous and organic layers are allowed to separate. After removing the aqueous layer, water (73 kg) is added to the organic layer and the mixture is stirred for 20 to 30 minutes. The aqueous layer is removed and organic layer is washed with water again (total 2.times.73 kg water). The organic layer is concentrated to approximately one-third of its original volume (~85 L) by vacuum distillation. After allowing the concentrate to equilibrate to room temperature and pressure, heptane (73 kg) is added over 45 to 60 minutes and the resulting slurry is stirred for about 1 hr. The slurry is then filtered, and the residual crystalline solid is washed with heptane (118 kg). The filter cake is dried in vacuo at 40 to 50.degree. C. for 8 to 16 hr to yield **S**-(-)-**amlodipine** free base (17.7 kg, 91.7% yield, 99.98% enantiomeric purity, >99.5% chemical purity).

CLM What is claimed is:

5. The method of claim 1, wherein the amlodipine hemitartrate dimethylacetamide monosolvate is enriched for **S**-(-)-**amlodipine** D-hemitartrate dimethylacetamide monosolvate.

15. A composition comprising crystalline **S**-(-)-**amlodipine** D-hemitartrate dimethylacetamide monosolvate, wherein at least 80% of the amlodipine in the composition is **S**-(-)-**amlodipine**.

16. The composition of claim 15, wherein at least 90% of the amlodipine in the composition is **S**-(-)-**amlodipine**.

17. The composition of claim 15, wherein at least 97% of the amlodipine in the composition is **S**-(-)-**amlodipine**.

18. A composition comprising crystalline **R**-(+)-**amlodipine** L-hemitartrate dimethylacetamide monosolvate, wherein at least 80% of the amlodipine in the composition is **R**-(+)-**amlodipine**.

19. The composition of claim 18, wherein at least 90% of the amlodipine in the composition is **R**-(+)-**amlodipine**.

20. The composition of claim 18, wherein at least 97% of the amlodipine in the composition is **R**-(+)-**amlodipine**.

26. The composition of claim 21, wherein at least 80% of the amlodipine in the composition is **S**-(+)-**amlodipine**.

27. A solid medicament tablet comprising crystalline amlodipine or a granular salt or hydrate thereof, and one or more pharmaceutically acceptable carriers, wherein at least 80% of the amlodipine in the composition is **S**-(+)**amlodipine**.

L3 ANSWER 14 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2003:64724 USPATFULL
TITLE: Novel therapeutic agents for membrane transporters
INVENTOR(S): Jenkins, Thomas E., La Honda, CA, UNITED STATES
Christensen, Burton G., Alamo, CA, UNITED STATES
Griffin, John H., Atherton, CA, UNITED STATES
Judice, J. Kevin, El Granada, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003044845	A1	20030306
APPLICATION INFO.:	US 2002-75017	A1	20020213 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-499176, filed on 7 Feb 2000, ABANDONED Continuation of Ser. No. US 1999-327096, filed on 7 Jun 1999, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-88465P	19980608 (60)
	US 1998-93068P	19980716 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: THERAVANCE, INC., 901 GATEWAY BOULEVARD, SOUTH SAN FRANCISCO, CA, 94080
NUMBER OF CLAIMS: 63
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 5827
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel multi-binding compounds (agents) are disclosed which bind cell membrane transporters including ion channels, molecular transporters and ion pumps. The compounds of this invention comprise from 2 to 10 ligands each of which can bind to such cellular transporters to modulate the biological processes/functions thereof. Each of the ligands is covalently attached to a linker (framework) to provide for a multi-binding compound. The linker is selected such that the multi-binding compound exhibits increased modulation of the biological processes/functions of the transporter as compared to the aggregate of the individual ligand units made available for binding to the transporter.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD [0645]
TABLE 6

Activators and Inhibitors of Membrane Transporters

Transporter	Current and Potential Therapeutic Indication(s)	Drugs and Other Therapies
Ca.sup.2+ Channel		
L-Type	Angina, Atherosclerosis Cardiac failure,	Amlodipine, nimodipine, aranidipine, barnidipine,

	Hyperlipidemia	cilnidipine, efonidipine
	Hypertension, Peripheral vascular disease, Alzheimers disease, Cerebral infarction Cerebrovascular ischemia, Migraine, Prophylaxis of migraine, Subarachnoid hemorrhage, Renovascular	hydrochloride, lercanidipine, manidipine, nilvadipine, isradipine, AE-0047, azelnidipine, lemildipine, lomerizine, pranidipine, fantofarone, oxodipine, clevidipine, diperdipine,
Bay-t-		
	hypertension, Heart disease Central nervous system disease, Alzheimers disease, Motor neurone disease, Parkinsons disease, Reperfusion injury, Epilepsy, Dementia, Depression,	7207, AH-1058, AP-1067, CP-060S, CPC-301, CPC-317, GS-386, LCB-2514, LOE-908, LY-042826, MR-14134, NNC-09-0026, Org-13061, P-5, PCA-50922, PCA-50938, PCA-50941, RGH-2716, **S**-(-)-
amlodipine,		
	Epilepsy, Head Injury, Neuropathic pain, Cardiac failure, Cystic fibrosis, Hypercholesterolemia, Ocular disease, Parkinsons disease,	SANK-71996, semotiadil analogs, SIB-1281, SNX-124, SNX-111 (ziconotide), SNX-325, SNX-239, SNX-236, VUF-8929, zicontide analogs, felodipine
+		
	Neurodegenerative disease, Thromboembolism,	ramipril, vexibinol, docosahexaenoic acid,
lacidipine,		
	Subarachnoid hemorrhage, Inhibition of kinetic cell death, Pregnancy disorder, Osteoporosis	NS-21, bisaramil, SD-3212, BRL-32872, nifedipine, nifedipine, Nifelan, Verelan, semotiadil, S-312-d, CERM-12816, ipenoxazone, verapamil isomers, tamolarizine, SB-201823A, TDN-345, atosiban, TA-993, lifarizine, fasudil, furnidipine, elgodipine,
SKT-M-		
		26, Y-22516, Verex, verapamil, AIT-110, K-201, AIT-111, FPL-64176, NPS-568, L-366682, JTV-519, SNX-482, SKF-45675
T-Type	Angina, Cardiac failure Hypertension, Chronic stable angina pectoris, Stroke, Cerebrovascular ischemia	Mibefradil U-92032
N-Type	Cardiac failure, Cardiovascular disease, Neurodegenerative disease, Head injury, Brain injury, Cerebrovascular ischemia, Inflammation, Neuropathy Pain, neuropathic pain Hypertension, Inflammation Alzheimers disease, Parkinsons disease, Motor neuron disease, Epilepsy	SNX-111 (ziconotide), SNX-124, SNX-325, SNX-239, SNX-236, zicontide analogs, conotoxins, AM-336, PD-029361, PD-157667, PD-158143, A-53930A, conopeptides
K.sup.+ Channels Voltage Sensitive	Heart arrhythmia, Tachycardia, Ischemic heart disease, Cardiac failure, Transplant rejection,	SB-237376, GYKI-16036, KCB-295, KCB-328, KCB-345, KMC-IV-84, L-768673, PGE-8444384, pyridotriazoles, CK-4001,

	Autoimmune disease,	ibutilide, d-(+)-sotalol,
MS-551,		
	Diabetes mellitus, Sickle cell	azimilide, dofetilide,
sematilide,		
	anemia, Muscular dystrophy Gastrointestinal disease, Mental disorder, Sleep disorder, Alcoholism, Inflammation, Cerebrovascular ischemia, Myocardial infarction	E-4031, nibentan, GLG-V-13, WAY-123398, ersentilide, ATI-2001, L-735821, LY-190147, EGIS-7229, fampridine, CK-1649C, tedisamil, HMR-1883, L-755860, RX-871024, UCL-1495, UCL-1559, UCL-1684, UK-78282 derivatives,
alinidine		
		analogs, RSD10XX series, CPU-86017, TJN-505, Win-17317-3, stobadine
Ca2+ sensitive	Hypertension Heart arrhythmia CNS diseases	UCL-1530
Receptor-coupled	Epilepsy, Parkinsons disease Pain, Cerebrovascular,	Conopeptides JTV-519 KB-R7943, SM-20550, cariporide, amiloride,
RSD-921,		
		carsatrin, LY368052, BDF-9198, lamotrigine, stobadine, SD-3212, conopeptides
Cl.sup.- Channel	Cystic fibrosis, Sinusitis,	P-0822, GR-213487B,
	Helminth infection, Nematode	ivermectin, S-20787,
cytofectins		
	infection, Hypercholesterolemia, Carcinoma, Diarrhea, Keratosis, Neoplasm, Sickle cell anemia, Ischemia, Reperfusion injury, Hypertension, Head Injury, Cardiac failure	(CFTR), CFTR gene therapy; clotrimazole and analogs, AHC-93, CPC-701, CPC-702, OPC-18360
Monoamine Transporters (general)	Parkinson's disease, Central nervous system disease, Depression, Obesity	BTS-74398, NS-2389, sibutramine
Noradrenaline	Attention deficit hyperactivity-disorder, Depression, Nicotine use disorder, Psychosis, Parkinson's disease	Tomoxetine, BW-1555U88, demexiptiline
5-HT	Anxiety disorder, Depression Obsessive/compulsive disorder, Sleep disorder, Sexual dysfunction, Bulimia, Premenstrual syndrome,	Paroxetine, citalopram, fluvoxamine, tianeptine, fluoxetine, S-fluoxetine, R-fluoxetine, sertraline, dexfenfluramine, indalpine,
YM-		
	Psychosexual disorder, Infarction, Antiarrhythmic, Panic and post-traumatic	922, cericlamine, (S)-sibutramine, DuP-631, venlafaxine, paroxetine
analog,		
	stress disorder, Anorexia nervosa, Substance, dependence, Migraine, Alzheimer's disease, Pain, Incontinence, Micturition	roxindole, YM-992, S-9977, A-80426, venlafaxine, tramadol, duloxetine, milnacipran

	disorder	
Dopamine	Schizophrenia, Cocaine use disorder, Parkinson's disease Schizophrenia, Substance dependence	CDTP-30640, PR-000001, PR-000608, PR-000609, RTI-113, RTI-177, vanoxerine, WIN-35065 analogs, WF-23, GPI-2138
P-Glyco-protein	Neoplasm, Brain tumor, Breast tumor, Liver tumor, Neoplasm, Ovary tumor, Prostate tumor, Sarcoma, Carcinoma, Multidrug resistant infection, Lymphoma	VX-710, VX-853, cinchonine, GF-120918, LY-335979, XR-9576, MS-209, BRI MAb MDR-1, CP-114416, CP-117227, CR-10-11, GR-66234A, ISIS-7597 analogs, KT-5822Y, MRK-16, MRK-17, N-276-12, OC104-26, OC42-92, OC62-805, PAK-200, S-16317, SB-RA-31012, XR-1500, 10-deacetylbaccatin III derivatives, LY-329146, KT-5720, SDZ-280-446
Gastric	Esophagitis, Peptic ulcer,	(S)-lansoprazole,
pantoprazole,		
Proton	Duodenal ulcer, Stomach	rabeprazole, perprazole, H-
Pump	ulcer, Gastrointestinal disease, Peptic ulcer, Helicobacter pylori infection, Osteoporosis, Angina, Fungal infection,	33525, IY-81149, YH-1238, YH-1885, IY-81238, (-)-pantoprazole, AD-8240, bafilomycin and its
derivatives,		
	Myocardial infarction, Contraception, Cerebrovascular ischemia ischemia, Ischemia, Heart arrhythmia, Myocardial infarction, Cardioprotection	BY-112, FR-168888, scopadulcic acid B, SM-20220, UJ-2012, YS-2012 NC-1005
K.sub.ATP	Angina, Asthma, Hypertension, Incontinence Cerebrovascular ischemia, Ischemic heart disease, Cardiovascular disease, Hyperinsulinemia, Asthma, Epilepsy, Hypertension, Incontinence, Urinary dysfunction, Micturition disorder, Irritable bowel syndrome, Angina, Restenosis, Insulin dependent diabetes, Non-insulin dependent diabetes, Diabetic neuropathy, Anxiety disorder Neurosis, Subarachnoid hemorrhage, Alzheimers disease	JTV-506, Y-26763, Y-27152, ZD-6169, BMS-204352, KR-30450, MCC-134, ABA-267, BMS-182264, BPDZ-44, dehydrosoyasaponin-1, DY-9708, EMD-67618, KC-128, KC-332, KRN-4884, L-3, L-364373, LM-3339, maxikdiol, NIP-121, NN-5501, NS-8, RS-91309, S-103, SCA-40, U-89232, U-99751, WAY-135201, ZD-0947, ZM-244085, ZM-260384, nicorandil, KC-515, TAK-636, glipizide, KAD-1229, DMP-543, U-37883A, PNU-96293, PNU-99963, BTS-67582, levcromakalim, celikalim
Na.sup.+	Cardiovascular disease, Heart	Restacorin, Ro-22-9194,
Channel	arrhythmia, Tachycardia Infarction, CNS disorders Pain, Asthma, Affective neurosis, Autism, Cerebrovascular ischemia, Depression, Epilepsy, Huntingtons chorea, Seizure	alprafenone, BRB-I-28, recainam, antiarrhythmics, Nortran, CLN-93, RSD10XX series, E-047/1, moracizine, pilsicainide, pirmenol, lamotrigine, procaine hydrochloride,
Steroidogenesis,		
	Epilepsy, Convulsion, Huntingdon's chorea, Bipolar	bupivacaine, cLN-93, 4030W92, 4991W93, transcainide, GW-

disorder, Autism, Stroke, HIV infection, Topical anesthesia, Migraine, Depression, Central nervous system disease, Anesthesia, Urinary tract disease, Ulcerative colitis, local anesthetic in surgery, Cystic fibrosis, Parkinsons disease	273293, LTA, SL-90.0571, AAA-241, AWD-140-190, BW-202W92, GW-286103, iodoamiloride, lidocaine, PD-85639, QX-314, ropivacaine, fosphenytoin, NS-7, PNU-151774E, BW-618C89, conopeptides, JTV-519, lifarizine, EMD-96785, EMD-85131, EMD96875, FR-183998,

L3 ANSWER 15 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2003:38384 USPATFULL
TITLE: Resolution of the enantiomers of amlodipine
INVENTOR(S): Xitian, Zhang, JiLin, CHINA

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003028031	A1	20030206	
	US 6646131	B2	20031111	
APPLICATION INFO.:	US 2002-203615	A1	20020816	(10)
	WO 2000-CN538		20001208	

	NUMBER	DATE
PRIORITY INFORMATION:	CN 2000-12701	20000221

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JACOBSON HOLMAN PLLC, 400 SEVENTH STREET N.W., SUITE 600, WASHINGTON, DC, 20004
NUMBER OF CLAIMS: 3
EXEMPLARY CLAIM: 1
LINE COUNT: 191
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invitation provides an efficient method for the resolution of (R)-(+)-(formula (I)) and (S)-(-)(formula (II))-enantiomers of amlodipine, where the chiral reagent for resolution is tartaric acid and the chiral auxiliary reagent for resolution is deuterated dimethyl sulphoxide (DMSO-d6).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0002] (**S**)-(-)-**amlodipine** and its salts are long-acting calcium channel blockers, and are thus useful for the treatment of hypertension and angina and (**R**)-(+)-**amlodipine** also exhibits activity in the treatment or prevention of atherosclerosis. ##STR1##

SUMM [0005] The invention provides a feasible method for the separation of racemic amlodipine. The chiral reagent for separation is L-tartaric acid or D-tartaric acid and the chiral auxiliary reagent is hexadeuterium dimethyl sulphoxide (DMSO-d.sub.6), in the amlodipine and tartaric acid mole ratio of about 1:0.25. The resulting precipitate is (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 solvate or (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 solvate.

SUMM [0007] The above precipitate can further be treated to give (**R**)-(+)-**amlodipine** or (**S**)-(-)-**amlodipine**.

SUMM [0013] The crystalline precipitate constituent is (**S**)-(-)-**amlodipine**-hemi-tartrate-mono-DMSO-d.sub.6 solvate or **R**

-(+)-**amlodipine**-hemi-tartrate-mono-DMSO-d.sub.6 solvate respectively.

DETD (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 solvate and (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 solvate from (R, **S**)-**amlodipine**

DETD [0015] To a stirred solution of 5 g (R, **S**)-**amlodipine** in 22.9 g DMSO-d.sub.6 was added a solution of 0.458 g D-tartaric acid (0.25 mole equivalents) in 22.9 g DMSO-d.sub.6. Precipitation began within one minute, and the resulting slurry was stirred at room temperature overnight. The solid was collected by filtration, washing with 20 ml acetone. It was then dried at 50 in vacuo overnight to give 2.36 g (68% of theoretical yield) (**S**)-(-)-**amlodipine** -hemi-D-tartrate-mono-DMSO-d.sub.6 solvate, m.p. 158-160 (Found: C 50.81%, H(D) 7.09%, N 4.84%, C.sub.20H.sub.25N.sub.2O.sub.5Cl 0.5 C.sub.4H.sub.6O.sub.6 C.sub.2D.sub.6OS; Calc. for C 50.74%, H (D) 7.04%, N 4.90%), optical purity 99.9% d.e. by chiral HPLC.

DETD [0016] 0.44 g L-tartaric acid (0.25 mole equivalents) was added to the filtered fluid and stirred at room temperature overnight. The solid was collected by filtration, washing with 20 ml acetone. It was then dried at 50 in vacuo overnight to give 2.0 g (55% of theoretical yield) (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 solvate, m.p. 158-160 , (Found: C 50.67%, H (D) 6.95%, N 4.90%, C.sub.20H.sub.25N.sub.2O.sub.5Cl 0.5 C.sub.4H.sub.6O.sub.6 C.sub.2D.sub.6OS: Calc. for C 50.74%, H (D) 7.04%, N 4.93%), optical purity 99.5% d. e. by chiral HPLC.

DETD (**S**)-(-)-**amlodipine** from (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono- DMSO-d.sub.6 solvate

DETD [0017] 5 g (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 solvate and 56 ml 2N NaOH water solution were stirred together with 56 ml CH.sub.2Cl.sub.2 for 40 minutes. The organic solution was separated off and washed with water. The CH.sub.2Cl.sub.2 was distilled off and hexane was added and stirred to crystallize it. The solid was collected by filtration and dried at 50 in vacuo overnight to give 3.20 g (88% of theoretical yield) (**S**)-(-)-**amlodipine**, m.p. 107-110, (Found: C 58.69%, H 6.09%, N 6.84%; Calc. for C.sub.20H.sub.25N.sub.2O.sub.5Cl: C 58.75%, H 6.16%, N 6.85%), [ ].sub.D.sup.25-32.6 (C=1, MeOH), optical purity 99.9% e.e. by chiral HPLC.

DETD (**R**)-(+)-**amlodipine** from (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 solvate

DETD [0018] 5 g (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 solvate and 56 ml 2N NaOH water solution were stirred together with 56 ml CH.sub.2Cl.sub.2 for 40 minutes. The CH.sub.2Cl.sub.2 was distilled off and hexane was added and stirred to crystallize it. The solid was collected by filtration and dried at 50

DETD [0019] in vacuo overnight to give 3.31 g (91% of theoretical yield) (**R**)-(+)-**amlodipine**, m.p. 107-110, (Found: C 58.41%, H 6.05%, N 6.62%; Calc. for C.sub.20H.sub.25N.sub.2O.sub.5Cl: C 58.75%, H 6.16%, N 6.85%), [ ].sub.D.sup.25+32.6 (C=1, MeOH), optical purity 99.5% e.e. by chiral HPLC.

DETD (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 solvate and **R**-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 solvate from (R, **S**)-**amlodipine**.

DETD [0020] The method of example 1 was used, but substituting the DMSO-d.sub.6 with a mixed solvent and DMSO-d.sub.6/amlodipine 1 (mole ratio). V.sub.solvent/(V.sub.DMSO-d6+V.sub.solvent) was shown in percentages. (V.sub.DMSO-d6+V.sub.solvent)M=4.about.18, in which, V, volume, ml; solvent; M, mass of amlodipine, g. The solvate can then be processed to (**S**)-(-)-**amlodipine** and (**R**)-(+)- **amlodipine** according to the procedures of examples 2

and 3.

TABLE

Solvent	solvent %*	(S)-(-)-enantiomer % e.e.*	(R)-(+)-enantiomer % e.e.*
methylethyl ketone	2	99.0	98.7
toluene	2	92.0	91.7
Isopropyl alcohol	5	92.6	92.4
H.sub.2O	10	98.5	98.4
dimethyl acetamide	10	98.3	98.1
tetrahydrofuran	33	98.6	98.5
ethyl acetate	50	99.2	99.1
dichloromethane	50	100	99.8
diethyl sulphoxide	50	98.1	98.4
diethyl sulphoxide	72	91.1	90.5
dimethyl sulphoxide	90	94.5	94.1
acetone	50	99.2	99.0
acetone	70	95.7	96.1
acetone	90	95.4	95.7
acetone	97	96.8	96.5
acetone	99	95.4	95.1

*Measured by chiral HPLC.

DETD Benzene sulfonic acid (**S**)-(-)-**amlodipine**

DETD [0021] 5 g (**S**)-(-)-**amlodipine** was put into 120 ml water and 1.4 g benzene sulfonic acid was added and stirred, which was heated to 60 under protection of nitrogen. After dissolution, with stirring stopped, the solution was cooled to room temperature and then crystallized overnight. The solid was collected by filtration, washing with 20 ml water, and then the benzene sulfonic acid (**S**)-(-)-**amlodipine** was dried at 50 in vacuo overnight to give 6.2 g (90% of theoretical yield), (Found: C 54.85%, H 5.15%, N 5.58%; Calc. for C.sub.20H.sub.25N.sub.2O.sub.5Cl: C 54.72%, H 5.14%, N 5.34%), [ ].sub.D.sup.25-24.9 (C=1, MeOH), optical purity 99.9% e.e. by chiral HPLC.

DETD [0022] The invention provides a feasible method for the separation of racemic amlodipine, which uses hexadeuterium dimethyl sulphoxide as the chiral auxiliary reagent to separate the enantiomers of racemic amlodipine with a time separation in optical purities of up to 100% e.e. and in yield of up to 68%, this high pure (**S**)-(-)-**amlodipine** is higher security for patients. Hexadeuterium dimethyl sulphoxide is reclaimed without notable cost augment for its wastage, so susceptible of industrial application.

CLM What is claimed is:

1. It is a method for the separation of (R)-(+)- and (S)-(-)-isomers of amlodipine from mixtures thereof, which comprises the reaction of the mixture of isomers with either the chiral reagent D- or L-tartaric acid by about 0.25 mole ration of tartaric acid and amlodipine in the chiral auxiliary reagent of hexadeuterium dimethyl sulphoxide (DMSO-d.sub.6) or in an organic solvent containing DMSO-d.sub.6 for the precipitation of, respectively, a DMSO-d.sub.6 solvate of D-tartrate salt of (**S**)-(-)-**amlodipine**, or a DMSO-d.sub.6 solvate of a L-tartrate salt of (**R**)-(+)-**amlodipine**.

3. The method according to any one of the preceding claims, wherein the solvate precipitated is, respectively, (**S**)-(-)-**amlodipine**-hemi-D-tartrate- mono-DMSO-d.sub.6-solvate or (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono

-DMSO-d.sub.6-solvate.

L3 ANSWER 16 OF 28 USPATFULL on STN

ACCESSION NUMBER:	2002:157675 USPATFULL			
TITLE:	Mutual prodrug of amlodipine and atorvastatin			
INVENTOR(S):	Crook, Robert James, Sandwich, UNITED KINGDOM Pettman, Alan John, Sandwich, UNITED KINGDOM			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2002082282	A1	20020627	
	US 6737430	B2	20040518	
APPLICATION INFO.:	US 2001-985	A1	20011031	(10)
	NUMBER		DATE	
PRIORITY INFORMATION:	GB 2000-27410		20001109	
	US 2000-255025P		20001212	(60)
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	Gregg C. Benson, Pfizer Inc., Patent Department, MS 4159, Eastern Point Road, Groton, CT, 06340			
NUMBER OF CLAIMS:	49			
EXEMPLARY CLAIM:	1			
LINE COUNT:	1100			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a mutual prodrug of amlodipine and atorvastatin, pharmaceutically acceptable acid addition salts thereof, pharmaceutical compositions thereof and the use of said prodrug and its salts in the manufacture of medicaments for the treatment of atherosclerosis, angina pectoris, combined hypertension and hyperlipidaemia and the management of cardiac risk.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0110] A solution of **R**(-)-**amlodipine** (840 mg, 2 mmol) and atorvastatin free acid (predominantly as the lactone) (1 g, 1.8 mmol) in ethanol (30 ml) was refluxed for 18 hours. The solvent was then evaporated in vacuo and the resulting oil purified by column chromatography using a standard silica column and eluting with 100% dichloromethane changing to 95%/5% dichloromethane/methanol. The desired product was obtained as a white foam (1.35 g, 76%). NMR (DMSO) d: 1.16-1.19 (t, 3H), 1.38-1.48 (m, 2H), 1.42-1.46 (d, 6H), 1.60-1.68 (m, 2H), 2.23-2.37 (d, 2H), 2.36 (s, 3H), 3.25-3.32 (m, 1H), 3.32-3.36 (m, 2H), 3.52-3.56 (m, 2H), 3.58-3.65 (m, 1H), 3.80-3.98 (m, 2H), 3.91-3.93 (m, 1H), 3.56 (s, 3H), 4.00-4.02 (m, 2H), 4.59-4.69 (d, 2H), 4.65 (s, 1H), 4.77 (s, 1H), 5.36 (s, 1H), 7.02-7.05 (m, 1H), 7.07-7.14 (m, 5H), 7.15-7.18 (m, 1H), 7.22-7.25 (m, 2H), 7.25-7.28 (m, 1H), 7.29-7.32 (m, 2H), 7.26-7.3 (m, 2H), 7.3-7.32 (m, 1H), 7.37-7.39 (m, 1H), 7.54-7.58 (d, 2H), 7.97 (t, 1H), 8.47 (s, 1H), 9.76 (s, 1H). MS (ESI): m/z [MNa.sup.+] 971.5 Na.sup.+ requires 971.5.

DETD [0113] A solution of **S**(+)-**amlodipine** (840 mg, 2 mmol) and atorvastatin free acid (predominantly as the lactone) (1 g, 1.8 mmol) in ethanol (30 ml) was refluxed for 18 hours. The solvent was then evaporated in vacuo and the resulting oil purified by column chromatography using a standard silica column and eluting with 100% dichloromethane changing to 95%/15% dichloromethane/methanol. The desired product was obtained as a white foam (1.14 g, 64%). NMR (DMSO) d: 1.16-1.19 (t, 3H), 1.38-1.48 (m, 2H), 1.42-1.46 (d, 6H), 1.60-1.68 (m, 2H), 2.23-2.37 (d, 2H), 2.36 (s, 3H), 3.25-3.32 (m, 1H), 3.32-3.36 (m, 2H), 3.52-3.56 (m, 2H), 3.58-3.65 (m, 1H), 3.80-3.98 (m, 2H),

3.91-3.93 (m, 1H), 3.56 (s, 3H), 4.00-4.02 (m, 2H), 4.59-4.69 (d, 2H), 4.65 (s, 1H), 4.77 (s, 1H), 5.36 (s, 1H), 7.02-7.05 (m, 1H), 7.07-7.14 (m, 5H), 7.15-7.18 (m, 1H), 7.22-7.25 (m, 2H), 7.25-7.28 (m, 1H), 7.29-7.32 (m, 2H), 7.26-7.3 (m, 2H), 7.3-7.32 (m, 1H), 7.37-7.39 (m, 1H), 7.54-7.58 (d, 2H), 7.97 (t, 1H), 8.47 (s, 1H), 9.76 (s, 1H). MS (ESI): m/z [MNa.sup.+] 971.4 Na.sup.+ requires 971.5.

L3 ANSWER 17 OF 28 USPATFULL on STN

ACCESSION NUMBER:	2002:141545 USPATFULL		
TITLE:	Methods of pharmacological treatment using **S** (-) **amlodipine**		
INVENTOR(S):	Foster, Robert T., Edmonton, CANADA		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002072532	A1	20020613
	US 6476058	B2	20021105
APPLICATION INFO.:	US 2001-987661	A1	20011115 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-433963, filed on 4 Nov 1999, PATENTED		
	NUMBER	DATE	
PRIORITY INFORMATION:	US 1998-107007P	19981104 (60)	
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Charles H. Jew, Mary Ann Dillahunty, Esq., BURNS, DOANE, SWECKER & MATHIS, L.L.P., P.O. Box 1404, Alexandria, VA, 22313-1404		
NUMBER OF CLAIMS:	2		
EXEMPLARY CLAIM:	1		
LINE COUNT:	975		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions are disclosed utilizing the optically pure S(-) isomer of amlodipine. This compound is a potent drug for the treatment of hypertension while avoiding the concomitant liability of adverse effects associated with the administration of the racemic mixture of amlodipine. The S(-) isomer of amlodipine is also useful for the treatment of angina and such other conditions as may be related to the activity of **S**(-) **amlodipine** as a calcium channel antagonist without the concomitant liability of adverse effects associated with the racemic mixture of amlodipine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Methods of pharmacological treatment using **S** (-) **amlodipine**

AB Methods and compositions are disclosed utilizing the optically pure S(-) isomer of amlodipine. This compound is a potent drug for the treatment of hypertension while avoiding the concomitant liability of adverse effects associated with the administration of the racemic mixture of amlodipine. The S(-) isomer of amlodipine is also useful for the treatment of angina and such other conditions as may be related to the activity of **S**(-) **amlodipine** as a calcium channel antagonist without the concomitant liability of adverse effects associated with the racemic mixture of amlodipine.

SUMM [0001] Pharmacological therapy utilizing pure formulations of **S** (-) **amlodipine** results in effective theraputic results while avoiding toxicities and adverse effects of racemic amlodipine. The methods and compositions described include the enriched deuterated forms of amlodipine as well as the nonenriched form. Amlodipine and deuteroamlodipine have a chiral center at C4 in the dihydropyridine

ring, and thus can exist as optical isomers. The isomers may be separated by various methods, for example selective crystallization and column chromatography. See for example T. Shibanuma, et al., Chem. Pharm. Bull., 28, 2809-2812 (1980). Alternatively, **S**(-) **amlodipine** may be prepared using optically active reactants, or by a combination of separation and chiral synthesis. Optical isomers of compounds are specified (+) or (-), indicating the direction the chiral center rotates a plane of polarized light.

SUMM [0006] The present commercial formulation of amlodipine contains the drug as the salt; amlodipine besylate. The term "amlodipine" herein refers to amlodipine and its pharmaceutically suitable salts and esters including amlodipine besylate and deuterated amlodipine and its pharmaceutically acceptable salts and esters including deuterated amlodipine besylate. This isomer will hereinafter be referred to as **S**(-) **amlodipine**. The terms "**S**(-) **amlodipine**" and "S(-) isomer of amlodipine" as used herein includes substantially optically pure **S**(-) **amlodipine** as well as optically pure **S**(-) **amlodipine**.

SUMM [0053] The methods and compositions of the present invention utilize the discovery that the optically pure S(-) isomer of amlodipine is an effective antihypertensive agent for both systolic and diastolic hypertension, particularly in mild to moderate disease and angina, which avoids the adverse effects including but not limited to headache and edema, dizziness, flushing, palpitation, fatigue, nausea, abdominal pain and somnolence which are associated with the administration of the racemic mixture of amlodipine. It has also been discovered that these novel compositions of matter containing optically pure **S**(-) **amlodipine** are useful in treating other conditions as may be related to the activity of **S**(-) **amlodipine** as a calcium channel antagonist, including but not limited to cerebral ischemia, cerebral disorders, arrhythmias, cardiac hypertrophy, heart failure, coronary vasospasm, myocardial infarction, renal impairment, viral infection, thrombosis, atherosclerosis, peripheral vascular disease, migraine headache, restenosis following vascular surgery or injury and acute renal failure while avoiding the above-described adverse effects associated with the administration of the racemic mixture of amlodipine. The present invention also includes methods for treating the above-described conditions in a human while avoiding the adverse effects that are associated with the racemic mixture of amlodipine by administering the S(-) isomer of amlodipine to said human.

DETD [0056] The present invention encompasses a method of treating hypertension in a human while avoiding the concomitant liability of adverse effects associated with the racemic mixture of amlodipine, which comprises administering to a human in need of such anti-hypertensive therapy, an amount of **S**(-) **amlodipine** or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate hypertension, but insufficient to cause said adverse effects associated with administration of racemic amlodipine.

DETD [0057] The present invention also encompasses an pharmaceutical composition for treatment of hypertension, in a human in need of anti-hypertensive therapy, which comprises an amount of **S**(-) **amlodipine** or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate hypertension but insufficient to cause adverse effects of racemic amlodipine. The calcium channel blocking composition may optionally contain a pharmaceutically acceptable carrier.

DETD [0058] The present invention further encompasses a method of treating

angina in a human, while avoiding the concomitant liability of adverse effects associated with the administration of racemic amlodipine, which comprises administering to a human in need of anti-angina therapy, an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate angina but insufficient to cause said adverse effects associated with administration of racemic amlodipine.

DETD [0059] In addition, the present invention encompasses an pharmaceutical composition for the treatment of a human having angina, which comprises an amount of **S**(-) **amlodipine** or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate angina but insufficient to cause adverse effects associated with the administration of racemic amlodipine. The antianginal composition may optionally contain a pharmaceutically acceptable carrier.

DETD [0060] A further aspect of the present invention includes a method of treating a condition caused by excessive calcium influx in cells in a human, while avoiding the concomitant liability of adverse effects associated with the administration of racemic amlodipine, which comprises administering to a human in need of a reduction in excessive calcium influx, an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate or prevent excessive calcium influx in cells but insufficient to cause said adverse effects associated with the administration of racemic amlodipine. Conditions caused by excessive calcium influx in cells in a human include, but are not limited to, cerebral ischemia, cerebral disorders such as cognitive disorders including but not limited to Alzheimer's dementia and memory impairment, retinal ischemia, viral infection, thrombosis, athersclerosis, arrhythmias, cardiac hypertrophy, congestive heart failure, coronary vasospasm, migraine, bronchospasm and asthma, Raynaud's phenomenon, myocardial infarction, renal impairment, restenosis following vascular surgery or injury and acute renal failure.

DETD [0061] The invention also includes a pharmaceutical composition for treating a condition caused by excessive calcium influx in cells in a human, which comprises an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said condition but insufficient to cause adverse effects associated with the administration of racemic amlodipine. This pharmaceutical composition may optionally contain a pharmaceutically acceptable carrier.

DETD [0065] The term "substantially free of its R(+) stereoisomer" as used herein means that the composition contains a greater proportion or percentage of the S(-) isomer of amlodipine in relation to the R(+) isomer of amlodipine, said percentage being based on the total amount of amlodipine in the composition. In a preferred embodiment the term "substantially free of its R(+) stereoisomer" means that the composition contains at least 90% by weight of **S**(-) **amlodipine**, and 10% by weight or less of **R**(+) **amlodipine**. In the most preferred embodiment the term "substantially free of the R(+) stereoisomer" means that the composition contains at least 99% by weight **S**(-) **amlodipine**, and 1% or less of **R**(+) **amlodipine**. In another preferred embodiment the term "substantially free of its R(+) stereoisomer" as used herein means that the composition contains about 100% by weight of **S**(-) **amlodipine**. The terms "substantially optically pure S(-) isomer of amlodipine" and "optically pure S(-) isomer of amlodipine" are also encompassed by the above-described meanings.

DETD [0069] Optically pure **S**(-) **amlodipine** can be prepared in a number of ways. Among these methods, the resolution of a

racemic mixture of amlodipine or its precursors and the asymmetric synthesis of amlodipine or precursors thereof are particularly useful. Resolution of a racemic mixture by fractional crystallization of diastereomeric derivatives or salts is perhaps the most straightforward method for obtaining optically pure **S**(-) **amlodipine**.

DETD [0071] Amlodipine is a basic compound and therefore diastereomeric salts suitable for separation by fractional crystallization are readily formed by the addition of chiral acid resolving agents in optically pure form to racemic amlodipine. Suitable resolving agents for use here include optically pure tartaric acid and its derivatives, camphorsulfonic acid, mandelic acid and derivatives thereof, and other optically active acids. The desired **S**(-) **amlodipine** isomer may be recovered either from the crystallized diastereomer or from the mother liquor, depending on the solubility properties of the particular acid resolving agent employed and depending on the particular acid enantiomer used. The identity of the **S**(-) **amlodipine** isomer so obtained may be confirmed by polarimetry and other analytical methods.

DETD [0072] A particular preferred means of obtaining **S**(-) **amlodipine** is based on the fractional crystallization of diastereomeric mixtures formed by basic resolving agents and racemic carboxylic-acid-containing precursors of amlodipine. See, for example, T. Shibanuma et al., Chem. Pharm. Bull. 28(9): 2809-2812 (1980) (who resolved the structurally related dihydropyridine nicardipine) and M. Eltze et al., Chirality 2: 233-240 (1990) and references cited therein. In particular, **S**(-) **amlodipine** is obtained by means of resolution of the corresponding racemic 4-aryl-1-ethoxymethyl-1,4-dihydro-5-methoxycarbonyl-2,6-dimethylpyridine-3-carboxylic acids by means of crystallization of the diastereomeric salts formed upon addition of basic resolving agents to the racemic precursor-followed by subsequent alkylation and esterification as described in International Patent Applications WO 88/07524 and WO 88/07525, Byk Gulden, 1988. Optically pure cinchonine and cinchonidine salts are basic resolving agents that have proven useful in the resolution of the dihydropyridines including amlodipine.

DETD [0073] The chemical synthesis of the racemic mixture of amlodipine can be performed by the method described in U.S. Pat. No. 4,572,909 and 5,438,145 as well as by other means known to those skilled in the art. The racemic acid ester is converted to its cinchonidine salt in methanol solution. Upon dilution with water and standing at room temperature, a crystalline precipitate is formed which can be subsequently recrystallized to constant rotation to give the diastereomerically pure cinchonidine salt. Further, the mother liquids from the original crystallization can be reduced in volume and stirred at room temperature, e.g., overnight, to afford a fine precipitate which can also be recrystallized to give the diastereomerically pure cinchonidine salt. The cinchonidine salt is partitioned between ethyl acetate and dilute hydrochloric acid to liberate the enantiomerically pure acid. The acid is then esterified using carbonyldiimidazole (CDI) and ethanolic sodium ethoxide, yielding **S**(-) **amlodipine**.

DETD [0075] In one embodiment of the present method, the optically pure S(-) isomer of amlodipine is administered to an individual suffering from hypertension. For example, **S**(-) **amlodipine** is administered therapeutically to an individual to reduce or ameliorate hypertension. In another embodiment, optically pure **S**(-) **amlodipine** can be administered prophylactically to reduce the probability of occurrence of hypertension

DETD [0077] **S**(-) **amlodipine** and its pharmaceutically acceptable salts and esters and deuterated amlodipine and pharmaceutically salts and esters of the present invention can be used to prepare pharmaceutical compositions useful in the treatment of the diseases and conditions discussed above. In these treatment regimens, a

therapeutic amount of **S**(-) **amlodipine** (salts, esters and deuterated derivatives) can be administered in admixture with a pharmaceutically acceptable non-toxic carrier. A therapeutically effective amount is that amount which, when administered to a mammal in need thereof, is sufficient to effect treatment, as defined above. Thus, the level of the drug in the formulation can vary from about 5 percent weight (% w) to about 95% w of the drug based on the total formulation and about 5% w to 95% w excipient. Preferably the drug is present at a level of about 10% w to about 70% w.

DETD [0079] In the practice of the above described method of the present invention a therapeutically effective amount of the **S**(-) **amlodipine** or a pharmaceutical composition containing same is administered via any of the usual and acceptable methods known in the art, either singly or in combination with other pharmaceutical agents. These compounds or compositions can thus be administered orally, systemically (e.g., transdermally, intranasally or by suppository) or parenterally (e.g., intramuscularly, subcutaneously and intravenously), and can be administered either in the form of solid or liquid dosages including tablets, solutions, suspensions, aerosols, and the like, as discussed in more detail above. It is preferred to administer **S**(-) **amlodipine** orally.

DETD [0084] The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids. Optionally, ester analogues of **S**(-) **amlodipine** may be used in the present invention.

CLM What is claimed is:

1. A method for blocking calcium channels, while avoiding the concomitant liability of adverse effects associated with administration of racemic amlodipine, which comprises administering to an animal in need of calcium channel blocking therapy, an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to provide calcium channel blockade but insufficient to cause said adverse effects of racemic amlodipine.

L3 ANSWER 18 OF 28 USPATFULL on STN

ACCESSION NUMBER:	2002:85603 USPATFULL		
TITLE:	Therapeutic compositions comprising excess enantiomer		
INVENTOR(S):	Chahwala, Suresh Babubhai, Kent, UNITED KINGDOM Dodd, Michael George, Kent, UNITED KINGDOM Humphrey, Michael John, Kent, UNITED KINGDOM		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002045648	A1	20020418
APPLICATION INFO.:	US 2001-930330	A1	20010815 (9)
	NUMBER		DATE
PRIORITY INFORMATION:	GB 2000-20842		20000823
	US 2000-237168P		20001002 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	APPLICATION		
LEGAL REPRESENTATIVE:	Gregg C. Benson, Pfizer Inc., Patent Department, Eastern Point Road, MS 4159, Groton, CT, 06340		
NUMBER OF CLAIMS:	38		
EXEMPLARY CLAIM:	1		
LINE COUNT:	581		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is concerned with pharmaceutical compositions

comprising a mixture of amlodipine enantiomers, which compositions have both anti-hypertensive and additional cardiovascular properties derived respectively from their calcium channel-blocking activity and their ability to release vascular nitric oxide (NO).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD Preparation of **R**(+) **Amlodipine** Salts from Racemic Amlodipine Besylate

DETD [0055] (2) Preparation and Separation of **R**(+) **Amlodipine** Tartrate Diastereoisomer

DETD [0056] To the dimethyl sulphoxide solution of racemic amlodipine free base obtained in Step (1) was added a solution of L-tartaric acid (6.62 g, 0.044 mol, 0.25 equiv) in dimethyl sulphoxide (360 mL). The solution was stirred at ambient temperature for six hours and the resulting solid collected by suction filtration and washed with acetone (200 mL). (Note: it is important that the dimethyl sulphoxide be completely removed from the solid before the solid is washed with acetone.) The solid was dried in vacuo at 50.degree. C. overnight to give (**R**)-**amlodipine**-hemi-L-tartrate-DMSO-solvate (68.25 g) as a pale yellow, tacky solid. The filtrate was set aside and may be used in the isolation of (**S**)-**amlodipine** free base.

DETD [0057] (3) Preparation of **R**(+) **Amlodipine** Free Base

DETD [0058] To a solution of the (**R**)-**amlodipine** -hemi-L-tartrate-DMSO-solvate (68.25 g) obtained in Step (2) in methylene chloride (345 mL, 5 mL/g) was added a solution of 50% sodium hydroxide (73 mL) in water (72 mL). The solution was stirred at ambient temperature for 40 minutes. The layers were separated and the organic layer extracted with water (1.times.150 mL) and gravity filtered through a magnesium sulphate (25 g) bed. The magnesium sulphate was washed with methylene chloride (40 mL) and the methylene chloride removed on a rotary evaporator using a water aspirator. Heptane was added to the evaporation flask as the volume allowed. Eventually, all of the methylene chloride was removed and 600 mL of heptane was added to the flask. The resulting solid was collected by suction filtration, washed with heptane and dried in vacuo at 50.degree. C. overnight to give (**R**)-**amlodipine** free base (19.4 g, 53.4% yield) as an off-white solid.

Chemical purity by HPLC: 99.95%
Chiral purity by HPLC: 98.88%

DETD [0061] To a solution of the (**R**)-**amlodipine** free base (1.0 g, 2.45 mmol) obtained in Step (3) in ethanol (15 mL) was added succinic acid (0.29 g, 2.45 mmol) in ethanol (8 mL). The mixture was allowed to stand at ambient t temperature overnight. The resulting solid was collected by suction filtration, rinsed with cold ethanol and dried in vacuo at 40.degree. C. overnight. An additional 6 hours in vacuo at 60.degree. C. gave the (**R**)-**amlodipine** succinate (1.11 g, 86.0% yield) as a white solid.

DETD [0063] (**R**)-**Amlodipine** free base (1.0 g, 2.45 mmol) obtained in Step (3) was dissolved in isopropyl alcohol (23 mL) after fifteen minutes stirring at ambient temperature. Methanesulphonic acid (0.24 g, 2.45 mmol) in isopropyl alcohol (2 mL) was added and the solution stirred at ambient temperature for 3 hours. After cooling in the refrigerator overnight, a small amount of solid had formed which amount slightly increased after a further night in the freezer. The solid was collected by suction filtration, rinsed with cold isopropyl alcohol and dried in vacuo at 40.degree. C. overnight. Drying in vacuo at 80.degree. C. overnight gave the (**R**)-**amlodipine** mesylate (1.08 g, 87.4% yield) as a beige solid.

DETD Preparation of **S**(-) **Amlodipine** Salts from Racemic

Amlodipine Besylate

DETD [0064] **S**(-) **amlodipine** succinate and **S**(-) **amlodipine** mesylate may be prepared in analogous fashion using, for example, D-tartaric acid rather than L-tartaric acid in Step (2) to prepare and isolate the corresponding diastereoisomer. Alternatively, the L-tartaric disastereoisomer may be worked up from the liquors left after isolation of the R(+) diastereoisomer.

L3 ANSWER 19 OF 28 USPATFULL on STN

ACCESSION NUMBER:	2001:235265 USPATFULL
TITLE:	Methods of pharmacological treatment using **S**(-) **amlodipine**
INVENTOR(S):	Foster, Robert T., Edmonton, Canada
PATENT ASSIGNEE(S):	Isotechnika, INC, Edmonton, Canada (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6333342	B1	20011225
APPLICATION INFO.:	US 1999-433963		19991104 (9)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Criares, Theodore J.
ASSISTANT EXAMINER:	Kim, Jennifer
LEGAL REPRESENTATIVE:	Burns, Doane, Swecker & Mathis, L.L.P.
NUMBER OF CLAIMS:	4
EXEMPLARY CLAIM:	1
LINE COUNT:	983

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions are disclosed utilizing the optically pure S(-) isomer of amlodipine. This compound is a potent drug for the treatment of hypertension while avoiding the concomitant liability of adverse effects associated with the administration of the racemic mixture of amlodipine. The S(-) isomer of amlodipine is also useful for the treatment of angina and such other conditions as may be related to the activity of **S**(-) **amlodipine** as a calcium channel antagonist without the concomitant liability of adverse effects associated with the racemic mixture of amlodipine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Methods of pharmacological treatment using **S**(-) **amlodipine**

AB Methods and compositions are disclosed utilizing the optically pure S(-) isomer of amlodipine. This compound is a potent drug for the treatment of hypertension while avoiding the concomitant liability of adverse effects associated with the administration of the racemic mixture of amlodipine. The S(-) isomer of amlodipine is also useful for the treatment of angina and such other conditions as may be related to the activity of **S**(-) **amlodipine** as a calcium channel antagonist without the concomitant liability of adverse effects associated with the racemic mixture of amlodipine.

SUMM Pharmacological therapy utilizing pure formulations of **S**(-) **amlodipine** results in effective theraputic results while avoiding toxicities and adverse effects of racemic amlodipine. The methods and compositions described include the enriched deuterated forms of amlodipine as well as the nonenriched form. Amlodipine and deuteroamlodipine have a chiral center at C4 in the dihydropyridine ring, and thus can exist as optical isomers. The isomers may be separated by various methods, for example selective crystallization and column chromatography. See for example T. Shibanuma, et al., Chem. Pharm. Bull., 28, 2809-2812 (1980). Alternatively, **S**(-)

amlodipine may be prepared using optically active reactants, or by a combination of separation and chiral synthesis. Optical isomers of compounds are specified (+) or (-), indicating the direction the chiral center rotates a plane of polarized light.

SUMM The present commercial formulation of amlodipine contains the drug as the salt; amlodipine besylate. The term "amlodipine" herein refers to amlodipine and its pharmaceutically suitable salts and esters including amlodipine besylate and deuterated amlodipine and its pharmaceutically acceptable salts and esters including deuterated amlodipine besylate. This isomer will hereinafter be referred to as **S**(-) **amlodipine**. The terms "**S**(-) **amlodipine**" and "S(-) isomer of amlodipine" as used herein includes substantially optically pure **S**(-) **amlodipine** as well as optically pure **S**(-) **amlodipine**.

SUMM The methods and compositions of the present invention utilize the discovery that the optically pure S(-) isomer of amlodipine is an effective antihypertensive agent for both systolic and diastolic hypertension, particularly in mild to moderate disease and angina, which avoids the adverse effects including but not limited to headache and edema, dizziness, flushing, palpitation, fatigue, nausea, abdominal pain and somnolence which are associated with the administration of the racemic mixture of amlodipine. It has also been discovered that these novel compositions of matter containing optically pure **S**(-) **amlodipine** are useful in treating other conditions as may be related to the activity of **S**(-) **amlodipine** as a calcium channel antagonist, including but not limited to cerebral ischemia, cerebral disorders, arrhythmias, cardiac hypertrophy, heart failure, coronary vasospasm, myocardial infarction, renal impairment, viral infection, thrombosis, atherosclerosis, peripheral vascular disease, migraine headache, restenosis following vascular surgery or injury and acute renal failure while avoiding the above-described adverse effects associated with the administration of the racemic mixture of amlodipine. The present invention also includes methods for treating the above-described conditions in a human while avoiding the adverse effects that are associated with the racemic mixture of amlodipine by administering the S(-) isomer of amlodipine to said human.

SUMM The present invention encompasses a method of treating hypertension in a human while avoiding the concomitant liability of adverse effects associated with the racemic mixture of amlodipine, which comprises administering to a human in need of such anti-hypertensive therapy, an amount of **S**(-) **amlodipine** or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate hypertension, but insufficient to cause said adverse effects associated with administration of racemic amlodipine.

SUMM The present invention also encompasses an pharmaceutical composition for treatment of hypertension, in a human in need of anti-hypertensive therapy, which comprises an amount of **S**(-) **amlodipine** or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate hypertension but insufficient to cause adverse effects of racemic amlodipine. The calcium channel blocking composition may optionally contain a pharmaceutically acceptable carrier.

SUMM The present invention further encompasses a method of treating angina in a human, while avoiding the concomitant liability of adverse effects associated with the administration of racemic amlodipine, which

comprises administering to a human in need of anti-angina therapy, an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate angina but insufficient to cause said adverse effects associated with administration of racemic amlodipine.

SUMM In addition, the present invention encompasses an pharmaceutical composition for the treatment of a human having angina, which comprises an amount of **S**(-) **amlodipine** or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate angina but insufficient to cause adverse effects associated with the administration of racemic amlodipine. The antianginal composition may optionally contain a pharmaceutically acceptable carrier.

SUMM A further aspect of the present invention includes a method of treating a condition caused by excessive calcium influx in cells in a human, while avoiding the concomitant liability of adverse effects associated with the administration of racemic amlodipine, which comprises administering to a human in need of a reduction in excessive calcium influx, an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate or prevent excessive calcium influx in cells but insufficient to cause said adverse effects associated with the administration of racemic amlodipine. Conditions caused by excessive calcium influx in cells in a human include, but are not limited to, cerebral ischemia, cerebral disorders such as cognitive disorders including but not limited to Alzheimer's dementia and memory impairment, retinal ischemia, viral infection, thrombosis, atherscleresis, arrhythmias, cardiac hypertrophy, congestive heart failure, coronary vasospasm, migraine, bronchospasm and asthma, Raynaud's phenomenon, myocardial infarction, renal impairment, restenosis following vascular surgery or injury and acute renal failure.

SUMM The invention also includes a pharmaceutical composition for treating a condition caused by excessive calcium influx in cells in a human, which comprises an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said condition but insufficient to cause adverse effects associated with the administration of racemic amlodipine. This pharmaceutical composition may optionally contain a pharmaceutically acceptable carrier.

SUMM The term "substantially free of its R(+) stereoisomer" as used herein means that the composition contains a greater proportion or percentage of the S(-) isomer of amlodipine in relation to the R(+) isomer of amlodipine, said percentage being based on the total amount of amlodipine in the composition. In a preferred embodiment the term "substantially free of its R(+) stereoisomer" means that the composition contains at least 90% by weight of **S**(-) **amlodipine**, and 10% by weight or less of **R**(+) **amlodipine**. In the most preferred embodiment the term "substantially free of the R(+) stereoisomer" means that the composition contains at least 99% by weight **S**(-) **amlodipine**, and 1% or less of **R**(+) **amlodipine**. In another preferred embodiment the term "substantially free of its R(+) stereoisomer" as used herein means that the composition contains about 100% by weight of **S**(-) **amlodipine**. The terms "substantially optically pure S(-) isomer of amlodipine" and "optically pure S(-) isomer of amlodipine" are also encompassed by the above-described meanings.

SUMM Optically pure **S**(-) **amlodipine** can be prepared in a number of ways. Among these methods, the resolution of a racemic mixture of amlodipine or its precursors and the asymmetric synthesis of amlodipine or precursors thereof are particularly useful. Resolution of a racemic mixture by fractional crystallization of diastereomeric derivatives or salts is perhaps the most straightforward method for obtaining optically pure **S**(-) **amlodipine**.

SUMM Amlodipine is a basic compound and therefore diastereomeric salts suitable for separation by fractional crystallization are readily formed by the addition of chiral acid resolving agents in optically pure form to racemic amlodipine. Suitable resolving agents for use here include optically pure tartaric acid and its derivatives, camphorsulfonic acid, mandelic acid and derivatives thereof, and other optically active acids. The desired **S**(-) **amlodipine** isomer may be recovered either from the crystallized diastereomer or from the mother liquor, depending on the solubility properties of the particular acid resolving agent employed and depending on the particular acid enantiomer used. The identity of the **S**(-) **amlodipine** isomer so obtained may be confirmed by polarimetry and other analytical methods.

SUMM A particular preferred means of obtaining **S**(-) **amlodipine** is based on the fractional crystallization of diastereomeric mixtures formed by basic resolving agents and racemic carboxylic-acid-containing precursors of amlodipine. See, for example, T. Shibanuma et al., Chem. Pharm. Bull. 28(9): 2809-2812 (1980) (who resolved the structurally related dihydropyridine nicardipine) and M. Eltze et al., Chirality 2: 233-240 (1990) and references cited therein. In particular, **S**(-) **amlodipine** is obtained by means of resolution of the corresponding racemic 4-aryl-1-ethoxymethyl-1,4-dihydro-5-methoxycarbonyl-2,6-dimethylpyridine-3-carboxylic acids by means of crystallization of the diastereomeric salts formed upon addition of basic resolving agents to the racemic precursor-followed by subsequent alkylation and esterification as described in International Patent Applications WO 88/07524 and WO 88/07525, Byk Gulden, 1988. Optically pure cinchonine and cinchonidine salts are basic resolving agents that have proven useful in the resolution of the dihydropyridines including amlodipine.

SUMM The chemical synthesis of the racemic mixture of amlodipine can be performed by the method described in U.S. Pat. No. 4,572,909 and 5,438,145 as well as by other means known to those skilled in the art. The racemic acid ester is converted to its cinchonidine salt in methanol solution. Upon dilution with water and standing at room temperature, a crystalline precipitate is formed which can be subsequently recrystallized to constant rotation to give the diastereomerically pure cinchonidine salt. Further, the mother liquids from the original crystallization can be reduced in volume and stirred at room temperature, e.g., overnight, to afford a fine precipitate which can also be recrystallized to give the diastereomerically pure cinchonidine salt. The cinchonidine salt is partitioned between ethyl acetate and dilute hydrochloric acid to liberate the enantiomerically pure acid. The acid is then esterified using carbonyldiimidazole (CDI) and ethanolic sodium ethoxide, yielding **S**(-) **amlodipine**.

SUMM In one embodiment of the present method, the optically pure S(-) isomer of amlodipine is administered to an individual suffering from hypertension. For example, **S**(-) **amlodipine** is administered therapeutically to an individual to reduce or ameliorate hypertension. In another embodiment, optically pure **S**(-)

amlodipine can be administered prophylactically to reduce the probability of occurrence of hypertension.

SUMM **S**(-) **amlodipine** and its pharmaceutically acceptable salts and esters and deuterated amlodipine and pharmaceutically salts and esters of the present invention can be used to prepare pharmaceutical compositions useful in the treatment of the diseases and conditions discussed above. In these treatment regimens, a therapeutic amount of **S**(-) **amlodipine** (salts, esters and deuterated derivatives) can be administered in admixture with a pharmaceutically acceptable non-toxic carrier. A therapeutically effective amount is that amount which, when administered to a mammal in need thereof, is sufficient to effect treatment, as defined above. Thus, the level of the drug in the formulation can vary from about 5 percent weight (%w) to about 95%w of the drug based on the total formulation and about 5%w to 95%w excipient. Preferably the drug is present at a level of about 10%w to about 70%w.

SUMM In the practice of the above described method of the present invention a therapeutically effective amount of the **S**(-) **amlodipine** or a pharmaceutical composition containing same is administered via any of the usual and acceptable methods known in the art, either singly or in combination with other pharmaceutical agents. These compounds or compositions can thus be administered orally, systemically (e.g., transdermally, intranasally or by suppository) or parenterally (e.g., intramuscularly, subcutaneously and intravenously), and can be administered either in the form of solid or liquid dosages including tablets, solutions, suspensions, aerosols, and the like, as discussed in more detail above. It is preferred to administer **S**(-) **amlodipine** orally.

SUMM The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids. Optionally, ester analogues of **S**(-) **amlodipine** may be used in the present invention.

CLM What is claimed is:

1. A method for blocking calcium channels, while avoiding the concomitant liability of adverse effects associated with administration of racemic amlodipine, which comprises administering to an animal in need of calcium channel blocking therapy, an amount of deuterated **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, wherein the deuterated **S**(-) **amlodipine** or salt thereof, comprises an amlodipine selected from the genus described by: ##STR2## wherein R represents either hydrogen or deuterium, and at least one R is deuterium; and wherein R.sup.1 represents either hydrogen or deuterium, and at least one R.sup.1 is deuterium, said amount being sufficient to provide calcium channel blockade but insufficient to cause said adverse effects of racemic amlodipine.

2. A compound comprising deuterated **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of the R(+) stereoisomer, wherein the deuterated **S**(-) **amlodipine** or salt thereof, comprises an amlodipine selected from the genus described by: ##STR3## wherein R represents either hydrogen or deuterium, and at least one R is deuterium; and wherein R.sup.1 represents either hydrogen or deuterium, and at least one R.sup.1 is deuterium.

L3 ANSWER 20 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2000:80769 USPATFULL
TITLE: Inhibition of smooth muscle cell migration by (**R)-amlodipine**
INVENTOR(S): Chahwala, Suresh Bababhai, Sandwich, United Kingdom
Winslow, Derek Paul, Sandwich, United Kingdom
PATENT ASSIGNEE(S): Pfizer Inc., New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6080761		20000627	
	WO 9505822		19950302	
APPLICATION INFO.:	US 1996-596365		19960221	(8)
	WO 1994-EP2697		19940810	
			19960221	PCT 371 date
			19960221	PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1993-17773	19930826

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Criares, Theodore J.
LEGAL REPRESENTATIVE: Richardson, Peter C., Benson, Gregg C., Jones, James T.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1
LINE COUNT: 169

AB The R(+) isomer of amlodipine is a potent inhibitor of smooth muscle cell migration despite its lack of calcium channel-blocking activity. It is useful for treating atherosclerosis, re-stenosis after angioplasty and endometriosis.

TI Inhibition of smooth muscle cell migration by (**R**)-**amlodipine**

SUMM This assay was carried out with varying concentrations of test compound added to the culture. The compounds thus tested were the maleate salts of the racemic mixture of R(+) and **S**(-) **amlodipine**, the maleate salts of R(+) and **S**(-) **amlodipine** separately and the known calcium channel-blocking agents nitrendipine and verapamil.

DETD For administration to man in the curative or prophylactic treatment of conditions involving smooth muscle migration, oral doses of **R** (+) **amlodipine** or its salts may be in the range of 2-10 mg daily for an average adult patient (weighing 70 kg), that is a range similar to that used for amlodipine in the treatment of hypertension. However, the absence of cardiovascular effects allows administration of much larger doses than would be recommended for the calcium channel-blocking S(-) isomer or the racemate, with a correspondingly greater effect on cell migration. The oral dose of **R**(+) **amlodipine** or a salt thereof for the average adult patient may thus be 20 mg or more and up to 100 mg/day, or even greater. The actual dose used will be determined by a physician considering the age, weight, condition and medical history of the patient. For a typical adult patient individual tablets or capsules are likely to contain 1 to 100 mg of active compound, in a suitable pharmaceutical vehicle or carrier. Dosages for intravenous administration would be in the range of 1-20 mg of active compound per single dose as required. Thus, according to another aspect of the invention, there is provided a unit dose of a pharmaceutical composition substantially free of calcium

channel-blocking activity containing (for oral administration) from 1 mg to 100 mg, preferably 20 to 100 mg, of the R(+) isomer of amlodipine or a pharmaceutically acceptable salt thereof. A further aspect of the invention provides such a unit dose for intravenous administration containing from 1 to 20 mg of the R(+) isomer of amlodipine or salt thereof.

L3 ANSWER 21 OF 28 USPATFULL on STN
ACCESSION NUMBER: 2000:41183 USPATFULL
TITLE: Separation of the enantiomers of amlodipine via their diastereomeric tartrates
INVENTOR(S): Spargo, Peter Lionel, Sandwich, United Kingdom
PATENT ASSIGNEE(S): Pfizer Inc., New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6046338		20000404	
APPLICATION INFO.:	US 1998-71810		19980505	(9)
RELATED APPLN. INFO.:	Division of Ser. No. US 704612			

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1994-5833	19940324

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rotman, Alan L.
LEGAL REPRESENTATIVE: Richardson, Peter C., Benson, Gregg C., Jones, James T.
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
LINE COUNT: 372
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the separation of R-(+)- and S-(-)-isomers of amlodipine (I) from mixtures thereof, which comprises the reaction of the mixture of isomers with either L- or D-tartaric acid in an organic solvent containing sufficient dimethyl sulphoxide (DMSO) for the precipitation of, respectively, a DMSO, solvate of an L-tartate salt of **R**-(+)-**amlodipine**, or a DMSO solvate of a D-tartrate salt of **S**-(-)-**amlodipine**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for the separation of R-(+)- and S-(-)-isomers of amlodipine (I) from mixtures thereof, which comprises the reaction of the mixture of isomers with either L- or D-tartaric acid in an organic solvent containing sufficient dimethyl sulphoxide (DMSO) for the precipitation of, respectively, a DMSO, solvate of an L-tartate salt of **R**-(+)-**amlodipine**, or a DMSO solvate of a D-tartrate salt of **S**-(-)-**amlodipine**.

SUMM We herein describe a new, simple, economic and efficient process for preparing both enantiomers of amlodipine 1a and their salts, in unexpectedly good yield andenantiomeric purity. The invention provides a method for the separation of the R-(+)-and S-(-)-isomers of amlodipine from mixtures thereof, which comprises the reaction of the mixture of isomers with either L- or D-tartaric acid in an organic solvent containing sufficient dimethyl sulphoxide (DMSO) for the precipitation of, respectively, a DMSO solvate of an L-tartrate salt of **R**-(+)-**amlodipine**, or a DMSO solvate of a D-tartrate salt of **S**-(-)-**amlodipine**. The use of both tartaric acid and DMSO are essential to this unique separation process.

SUMM It is understood that L-tartaric acid can also be used, in which case it

is the **R**-(+)-**amlodipine** isomer which forms the precipitate. It is also to be understood that once the precipitate has been formed, it can be further treated in a number of ways, for example to provide the free base, as illustrated above, or to provide alternative salts and/or solvates of amlodipine isomers. It is also to be understood that by virtue of the fact that a separation (or partial separation) of a particular enantiomer takes place, the resulting filtrate is thereby enriched with the opposite enantiomer (antipode), which may also be processed further, in a similar manner. This proceeds particularly well when about 0.25 mole of tartaric acid is used per mole of amlodipine. Co-solvents can be used in the resolution step, and can contribute to economy, ease of handling, etc., with the proviso that DMSO is present in sufficient amount to allow precipitation of the DMSO solvate to take place.

DETD (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate from (R,**S**)-**amlodipine**

DETD To a stirred solution of 114.27 g (R,**S**)-**amlodipine** in 558 ml DMSO was added a solution of 21 g D-(-)-tartaric acid (0.5 mole equivalents) in 558 ml DMSO. Precipitation began within 5 minutes, and the resulting slurry was stirred at room temperature overnight. The solid was collected by filtration, washing with 500 ml DMSO followed by 500 ml acetone. It was then dried at 50.degree. C. in vacuo overnight to give 71.3 g (91% of theoretical yield) (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-solvate, m.p. 158-160.degree. C., (Found: C 51.28%, H 6.10%, N 4.93%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].C.sub.2 H.sub.6 OS: C 51.29%, H 6.10%, N 4.98%), 98% d.e. by chiral hplc.

DETD (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-monohydrate from (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-solvate

DETD 50 g (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate was dissolved in 250 ml refluxing methanol. On cooling, a solid precipitated, and the slurry was stirred overnight at room temperature. The solid was collected by filtration, washing with 150 ml methanol, then dried at 50.degree. C. in vacuo overnight to give 38.4 g (86%) (**S**)-(-)-**amlodipine**-hemi-D-tartrate-monohydrate, m.p. 134-137.degree. C., (Found: C 52.67%, H 6.25%, N 5.49%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].H.sub.2 O: C 52.64%, H 6.02%, N 5.58%/), 98% d.e. by chiral hplc.

DETD (S)-(-)-Amlodilpine from (**S**)-(-)-**amlodipine**-hemi-D-tartrate-monohydrate

DETD 30 g (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-monohydrate was slurried in 230 ml CH.sub.2 Cl.sub.2 and 230 ml 2N NaOH(aq) for 20 minutes. The organic solution was then separated off and washed once with water. The CH.sub.2 Cl.sub.2 was distilled off and replaced with hexane, giving a slurry. The solid was collected by filtration and dried at 50.degree. C. in vacuo overnight to give 21.6 g (88%) (**S**)-(-)-**amlodipine**, m.p. 108-110.degree. C., (Found: C 58.57%, H 6.37%, N 6.76%: Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl: C 58.75%, H 6.16%, N 6.85%), [.alpha.].sub.D.sup.25 -32.5.degree. (c=1,MeOH), 98.4% e.e. by chiral hplc.

DETD (**S**)-(-)-**Amlodipine** from (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-solvate

DETD 5 g (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate was slurried in 56 ml CH.sub.2 Cl.sub.2 and 56 ml 2N NaOH(aq) for 40 minutes. The organic solution was then separated and washed once with water. The CH.sub.2 Cl.sub.2 was distilled off and replaced with hexane, giving a slurry. The solid was collected by filtration and dried at 50.degree. C. in vayuo overnight to give 3.39 g (93%) (**S**)-(-)-**amlodipine**, m.p. 107-110.degree. C., (Found: C 58.31%, H

6.57%, N 6.50%: Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl: C 58.75%, H 6.16%, N 6.85%), [.alpha.].sub.D.sup.25 -28.5.degree. (c=1,MeOH), 97% e.e. by chiral hplc.

DETD (**R**)-(+)-**Amlodipine**-hemi-L-tartrate-mono-DMSO-solvate from (R,**S**)-**amlodipine**

DETD To a stirred solution of 114.27 g(R,**S**)**amlodipine** in 558 ml DMSO was added a solution of 21.0 g (0.5 mole equivalents) L-(-)-tartaric acid in 558 ml DMSO. Precipitation began within 5 minutes, and the resulting slurry was stirred at room temperature overnight. The solid was collected by filtration, washing with 500 ml DMSO followed by 500 ml acetone. It was then dried at 50.degree. in vacuo overnight to give 67.0 g (85% of theoretical yield) (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate, m.p. 159-161.degree. C., (Found: C 51.27%, H 6.08%, N 4.91%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].C.sub.2 H.sub.6 OS: C 51.29%, H 6.10%, N 4.98%), 98% d.e. by chiral hpic.

DETD (**R**)-(+)-**Amlodipine**-hemi-L-tartrate-monohydrate from (**R**)-(+)-**amlodipine** hemi-L-tartrate-mono-DMSO-solvate

DETD 40g (**R**)-(+)-**Amlodipine**-hemi-L-tartrate-mono-DMSO-solvate was dissolved in 200 ml refluxing methanol. On cooling, a solid precipitated, and the slurry was stirred overnight at room temperature. The solid was collected by filtration, washing with 120 ml methanol, then dried at 50.degree. C. in vacuo overnight to give 30.0 g (84%) (**R**)-(+)-**amlodipine**-hemi-L-tartrate-monohydrate, m.p. 132-135.degree. C., (Found: C 52.68%, H 6.23%, N 5.46%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].H.sub.2 O: C 52.64%, H 6.02%, N 5.58%), 97.5% d.e. by chiral hpic.

DETD (**R**)-(+)-**Amlodipine** from (**R**)-(+)-**amlodipine**-hemi-L-tartrate-monohydrate

DETD 25 g (**R**)-(+)-**Amlodipine**-hemi-L-tartrate-monohydrate was slurried in 200 ml CH.sub.2 Cl.sub.2 and 200 ml 2N NaOH(aq) for 20 minutes. The organic solution was then separated off and washed once with water. The CH.sub.2 Cl.sub.2 was distilled off and replaced with hexane, giving a slurry. The solid was collected by filtration and dried at 50.degree. C. in vacuo overnight to give 17.8 g (87%) (**R**)-(+)-**amlodipine**, m.p. 108-110.degree. C., (Found: C 58.67%, H 6.24%, N 6.76%: Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl: C 58.75%, H 6.16%, N 6.85%), [.alpha.].sub.D.sup.25 +28.3.degree. (c=1, MeOH), 97.5% e.e. by chiral hplc.

DETD (**R**)-(+)-**Amlodipine** from (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate

DETD 5 g (**R**)-(+)-**Amlodipine**-hemi-L-tartrate-mono-DMSO-solvate was slurried in 56 ml CH.sub.2 Cl.sub.2 and 56 ml 2N NaOH(aq) for 40 minutes.

DETD The organic solution was then separated and washed once with water. The CH.sub.2 Cl.sub.2 was distilled off and replaced with hexane, giving a slurry. The solid was collected by filtration and dried at 50.degree. C. in vacuo overnight to give 3.43 g (94%) (**S**)(-)-**amlodipine**, m.p. 106-109.degree. C., (Found: C 58.26%, H 6.69%, N 6.43%: Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl: C 58.75%, H 6.16%, N 6.85%), [.alpha.].sub.D.sup.25 +29.90.degree. (c=1, MeOH), 98.5% e.e. by chiral hplc.

DETD (**S**)-(-)**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate and (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate from (R,**S**)-**amlodipine**

DETD To a stirred solution of 1.02 g of (R,**S**)-**amlodipine** in 5 ml of DMSO was added a slurry of 0.099 g (0.25 mole equivalents) of D-tartaric acid in 5 ml of DMSO. The resulting mixture was then left to stir overnight and the solid which formed was filtered off, washed with 2 ml of acetone and dried at 50.degree. C. in vacuo overnight to give

0.47 g (67% of theoretical yield) (**S**)-(-)-**amlodipine** hemi-D-tartrate-mono-DMSO-solvate; m.p. 159-162.degree. C., (Found: C 51.45%, H 6.13%, N 4.77%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].C.sub.2 H.sub.6 OS: C 51.29%, H 6.10%, N 4.98%), >99.5% d.e. by chiral hplc. To the filtrate was then added 0.099 g (0.25 mole equivalents) of L-tartaric acid, the mixture was then left to stir overnight and the solid formed filtered off and washed with 2 ml of acetone and dried at 50.degree. C. in vacuo to give 0.33 g (47% of theoretical yield) (**R**)-(+)-**amlodipine** -hemi-L-tartrate-mono-DMSO-solvate; m.p. 159-162.degree. C., (Found: C 51.49%, H 6.12%, N 4.85%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl. 0.5[C.sub.4 H.sub.6 O.sub.6].C.sub.2 H.sub.6 OS: C 51.29%, H 6.10%, N 4.98%), >99.5% d.e. by chiral hplc.

DETD (**S**)-(-)**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate and (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate from (R,**S**)-**amlodipine**

DETD Yield of (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-solvate=0.22 g (31% of theoretical yield) m.p. 160-163.degree. C., (Found C 51.13%, H 6.03%, N 4.91%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].C.sub.2 H.sub.6 OS:C 51.29%, H 6.10%, N 4.90%). 99.5% d.e. by chiral hplc.

DETD Yield of (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate=0.19 g (27% of theoretical yield), m.p. 160-163.degree. C., (Found: C 51.39%, H 6.01%, N 4.82%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].C.sub.2 H.sub.6 OS: C 51.29%, H 6.10%, N 4.98%), 98% d.e. by chiral hplc.

DETD (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate

DETD The method of Example 1 was repeated using the same molar ratios but using DMSO to which a co-solvent has been added as set out in the Table. The percentages are in v/v. The solvate can then be processed to **S**-(-)-**amlodipine** according to the procedures of Examples 2-4.

CLM What is claimed is:

1. A method for the separation of the R-(+)- and S-(-)-isomers of amlodipine from mixtures thereof, which comprises the reaction of the mixture of isomers with either L- or D-tartaric acid in an organic solvent containing sufficient dimethyl sulphoxide (DMSO) for the precipitation of, respectively, a DMSO solvate of an L-tartrate salt of **R**-(+)-**amlodipine**, or a DMSO solvate of a D-tartrate salt of **S**-(-)-**amlodipine**.

9. A process according to claim 1, wherein the solvate precipitated is, respectively, (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-solvate or (**R**)-(+)-**amlodipine** -hemi-L-tartrate-mono-DMSO-solvate.

L3 ANSWER 22 OF 28 USPATFULL on STN

ACCESSION NUMBER:	1998:51780 USPATFULL			
TITLE:	Separation of the enantiomers of amlodipine via their diastereomeric tartrates			
INVENTOR(S):	Spargo, Peter Lionel, Sandwich, United Kingdom			
PATENT ASSIGNEE(S):	Pfizer Inc., New York, NY, United States (U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5750707		19980512	
	WO 9525722		19950928	
APPLICATION INFO.:	US 1996-704612		19960918	(8)
	WO 1995-EP847		19950306	

19960918 PCT 371 date
19960918 PCT 102(e) date

	NUMBER	DATE
PRIORITY INFORMATION:	GB 1994-5833	19940324

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rotman, Alan L.
LEGAL REPRESENTATIVE: Richardson, Peter C., Benson, Gregg C., Jones, James T.
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1,2
LINE COUNT: 343
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the separation of R-(+)- and S-(-)-isomers of amlodipine (I) from mixtures thereof, which comprises the reaction of the mixture of isomers with either L- or D-tartaric acid in an organic solvent containing sufficient dimethyl sulphoxide (DMSO) for the precipitation of, respectively, a DMSO solvate of an L-tartrate salt of **R**-(+)-**amlodipine**, or a DMSO solvate of a D-tartrate salt of **S**-(-)-**amlodipine**. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method for the separation of R-(+)- and S-(-)-isomers of amlodipine (I) from mixtures thereof, which comprises the reaction of the mixture of isomers with either L- or D-tartaric acid in an organic solvent containing sufficient dimethyl sulphoxide (DMSO) for the precipitation of, respectively, a DMSO solvate of an L-tartrate salt of **R**-(+)-**amlodipine**, or a DMSO solvate of a D-tartrate salt of **S**-(-)-**amlodipine**. ##STR1##

SUMM We herein describe a new, simple, economic and efficient process for preparing both enantiomers of amlodipine 1a and their salts, in unexpectedly good yield and enantiomeric purity. The invention provides a method for the separation of the R-(+)-and S-(-)-isomers of amlodipine from mixtures thereof, which comprises the reaction of the mixture of isomers with either L- or D-tartaric acid in an organic solvent containing sufficient dimethyl sulphoxide (DMSO) for the precipitation of, respectively, a DMSO solvate of an L-tartrate salt of **R**-(+)-**amlodipine**, or a DMSO solvate of a D-tartrate salt of **S**-(-)-**amlodipine**. The use of both tartaric acid and DMSO are essential to this unique separation process.

SUMM It is understood that L-tartaric acid can also be used, in which case it is the **R**-(+)-**amlodipine** isomer which forms the precipitate. It is also to be understood that once the precipitate has been formed, it can be further treated in a number of ways, for example to provide the free base, as illustrated above, or to provide alternative salts and/or solvates of amlodipine isomers. It is also to be understood that by virtue of the fact that a separation (or partial separation) of a particular enantiomer takes place, the resulting filtrate is thereby enriched with the opposite enantiomer (antipode), which may also be processed further, in a similar manner. This proceeds particularly well when about 0.25 mole of tartaric acid is used per mole of amlodipine. Co-solvents can be used in the resolution step, and can contribute to economy, ease of handling, etc., with the proviso that DMSO is present in sufficient amount to allow precipitation of the DMSO solvate to take place.

DETD (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate from (R,**S**)-**amlodipine**

DETD To a stirred solution of 114.27 g (R,**S**)-**amlodipine**

in 558 ml DMSO was added a solution of 21 g D-(-)-tartaric acid (0.5 mole equivalents) in 558 ml DMSO. Precipitation began within 5 minutes, and the resulting slurry was stirred at room temperature overnight. The solid was collected by filtration, washing with 500 ml DMSO followed by 500 ml acetone. It was then dried at 50.degree. C. in vacuo overnight to give 71.3 g (91% of theoretical yield) (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-solvate, m.p. 158.degree.-160.degree. C., (Found: C 51.28%, H 6.10%, N 4.93%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.8 O.sub.6].multidot.C.sub.2 H.sub.6 OS: C 51.29%, H 6.10%, N 4.98%), 98% d.e. by chiral hplc.

DETD (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-monohydrate from (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-solvate

DETD 50 g (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate was dissolved in 250 ml refluxing methanol. On cooling, a solid precipitated, and the slurry was stirred overnight at room temperature. The solid was collected by filtration, washing with 150 ml methanol, then dried at 50.degree. C. in vacuo overnight to give 38.4 g (86%) (**S**)-(-)-**amlodipine**-hemi-D-tartrate-monohydrate, m.p. 134-137.degree. C., (Found: C 52.67%, H 6.25%, N 5.49%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].multidot.H.sub.2 O: C 52.64%, H 6.02%, N 5.58%), 98% d.e. by chiral hplc.

DETD (**S**)-(-)-**Amlodipine** from (**S**)-(-)-**amlodipine**-hemi-D-tartrate-monohydrate

DETD 30 g (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-monohydrate was slurried in 230 ml CH.sub.2 Cl.sub.2 and 230 ml 2N NaOH(aq) for 20 minutes. The organic solution was then separated off and washed once with water. The CH.sub.2 Cl.sub.2 was distilled off and replaced with hexane, giving a slurry. The solid was collected by filtration and dried at 50.degree. C. in vacuo overnight to give 21.6 g (88%) (**S**)-(-)-**amlodipine**, m.p. 108-110.degree. C., (Found: C 58.57%, H 6.37%, N 6.76%: Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl: C 58.75%, H 6.16%, N 6.85%), [.alpha.].sub.D.sup.25 -32.5.degree. (c=1, MeOH), 98.4% e.e. by chiral hplc.

DETD (**S**)-(-)-**Amlodipine** from (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-solvate

DETD 5 g (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate was slurried in 56 ml CH.sub.2 Cl.sub.2 and 56 ml 2N NaOH(aq) for 40 minutes. The organic solution was then separated and washed once with water. The CH.sub.2 Cl.sub.2 was distilled off and replaced with hexane, giving a slurry. The solid was collected by filtration and dried at 50.degree. C. in vacuo overnight to give 3.39 g (93%) (**S**)-(-)-**amlodipine**, m.p. 107-110.degree. C., (Found: C 58.31%, H 6.57%, N 6.50%: Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl: C 58.75%, H 6.16%, N 6.85%), [.alpha.].sub.D.sup.25 -28.5.degree. (c=1,MePH), 97% e.e. by chiral hplc.

DETD (**R**)-(+)-**Amlodipine**-hemi-L-tartrate-mono-DMSO-solvate from (R,**S**)-**amlodipine**

DETD To a stirred solution of 114.27 g(R,**S**)-**amlodipine** in 558 ml DMSO was added a solution of 21.0 g (0.5 mole equivalents) L-(-)-tartaric acid in 558 ml DMSO. Precipitation began within 5 minutes, and the resulting slurry was stirred at room temperature overnight. The solid was collected by filtration, washing with 500 ml DMSO followed by 500 ml acetone. It was then dried at 50.degree. in vacuo overnight to give 67.0 g (85% of theoretical yield) (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate, m.p. 159-161.degree. C., (Found: C 51.27%, H 6.08%, N 4.91%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].multidot.C.sub.2 H.sub.6 OS: C 51.29%, H 6.10%, N 4.98%), 98% d.e. by chiral hplc.

DETD (R)-(+)-**Amlodipine**-hemi-L-tartrate-monohydrate from (R)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate

DETD 40 g (R)-(+)-**Amlodipine**-hemi-L-tartrate-mono-DMSO-solvate was dissolved in 200 ml refluxing methanol. On cooling, a solid precipitated, and the slurry was stirred overnight at room temperature. The solid was collected by filtration, washing with 120 ml methanol, then dried at 50.degree. C. in vacuo overnight to give 30.0 g (84%) (R)-(+)-**amlodipine**-hemi-L-tartrate-monohydrate, m.p. 132-135.degree. C., (Found: C 52.68%, H 6.23%, N 5.46%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.5 O.sub.6].multidot.H.sub.2 O: C 52.64%, H 6.02%, N 5.58%), 97.5% d.e. by chiral hplc.

DETD (R)-(+)-**Amlodipine** from (R)-(+)-**amlodipine**-hemi-L-tartrate-monohydrate

DETD 25 g (R)-(+)-**Amlodipine**-hemi-L-tartrate-monohydrate was slurried in 200 ml CH.sub.2 Cl.sub.2 and 200 ml 2N NaOH(aq) for 20 minutes. The organic solution was then separated off and washed once with water. The CH.sub.2 Cl.sub.2 was distilled off and replaced with hexane, giving a slurry. The solid was collected by filtration and dried at 50.degree. C. in vacuo overnight to give 17.8 g (87%) (R)-(+)-**amlodipine**, m.p. 108-110.degree. C., (Found: C 58.67%, H 6.24%, N 6.76%: Calc. for C.sub.20 H.sub.25 N2O.sub.5 Cl: C 58.75%, H 6.16%, N 6.85%), [.alpha.].sub.D.sup.25 +28.3.degree. (c=1,MeOH), 97.5% e.e. by chiral hplc.

DETD (R)-(+)-**Amlodipine** from (R)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate

DETD 5 g (R)-(+)-**Amlodipine**-hemi-L-tartrate-mono-DMSO-solvate was slurried in 56 ml CH.sub.2 Cl.sub.2 and 56 ml 2N NaOH(aq) for 40 minutes.

DETD The organic solution was then separated and washed once with water. The CH.sub.2 Cl.sub.2 was distilled off and replaced with hexane, giving a slurry. The solid was collected by filtration and dried at 50.degree. C. in vacuo overnight to give 3.43 g (94%) (S)-(-)-**amlodipine**, m.p. 106-109.degree. C., (Found: C 58.26%, H 6.59%, N 6.43%: Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl: C 58.75%, H 6.16%, N 6.85%), [.alpha.].sub.D.sup.25 +29.9.degree. (c=1,MeOH), 98.5% e.e. by chiral hplc.

DETD (S)-(-)**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate and (R)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate from (R,S)-**amlodipine**

DETD To a stirred solution of 1.029 of (R,S)-**amlodipine** in 5 ml of DMSO was added a slurry of 0.099 g (0.25 mole equivalents) of D-tartaric acid in 5 ml of DMSO. The resulting mixture was then left to stir overnight and the solid which formed was filtered off, washed with 2 ml of acetone and dried at 50.degree. C. in vacuo overnight to give 0.47 g (67% of theoretical yield) (S)-(-)-**amlodipine** hemi-D-tartrate-mono-DMSO-solvate; m.p. 159-162.degree. C., (Found: C 51.45%, H 6.13%, N 4.77%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].multidot.C.sub.2 H.sub.6 OS: C 5.29%, H 6.10%, N 4.98%), >99.5% d.e. by chiral hplc. To the filtrate was then added 0.099 g (0.25 mole equivalents) of L-tartaric acid, the mixture was then left to stir overnight and the solid formed filtered off and washed with 2 ml of acetone and dried at 50.degree. C. in vacuo to give 0.33 g (47% of theoretical yield) (R)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate; m.p. 159-162.degree. C., (Found: C 51.49%, H 6.12%, N 4.85%; Calc. for C.sub.20 H.sub.25 N2O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].multidot.C.sub.2 H.sub.6 OS: C 51.29%, H 6.10%, N 4.98%), >99.5% d.e. by chiral hplc.

DETD (S)-(-)**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate and (R)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate from (R,S)-**amlodipine**

DETD Yield of (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-solvate=0.22 g (31% of theoretical yield) m.p. 160-163.degree. C., (Found C 51.13%, H 6.03%, N 4.91%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].multidot.C.sub.2 H.sub.6 OS:C 51.29%, H 6.10%, N 4.90%). 99.5% d.e. by chiral hplc.

DETD Yield of (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-solvate=0.19 g (27% of theoretical yield), m.p. 160-163.degree. C., (Found: C 51.39%, H 6.01%, N 4.82%; Calc. for C.sub.20 H.sub.25 N.sub.2 O.sub.5 Cl.0.5[C.sub.4 H.sub.6 O.sub.6].multidot.C.sub.2 H.sub.6 OS: C 51.29%, H 6.10%, N 4.98%), 98% d.e. by chiral hplc.

DETD (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate

DETD The method of Example 1 was repeated using the same molar ratios but using DMSO to which a co-solvent has been added as set out in the Table. The percentages are in v/v. The solvate can then be processed to **S**-(-)-**amlodipine** according to the procedures of Examples 2-4.

CLM What is claimed is:

1. (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-mono-DMSO-solvate.

2. (**R**)-(+)-**Amlodipine**-hemi-L-tartrate-mono-DMSO-solvate.

3. (**S**)-(-)-**Amlodipine**-hemi-D-tartrate-monohydrate.

4. (**R**)-(+)-**Amlodipine**-hemi-L-tartrate-monohydrate.

L3 ANSWER 23 OF 28 USPATFULL on STN

ACCESSION NUMBER:	96:43663 USPATFULL
TITLE:	Inclusion complexes of optically active 1,4-dihydropyridines with methyl-.beta.-cyclodextrin
INVENTOR(S):	Fercej-Temeljotov, Darja, Ljubljana, Spratly Islands Zmitek, Janko, Ljubljana, Spratly Islands Husu-Kovacevic, Breda, Ljubljana, Spratly Islands Kotnik, Sonja, Ljubljana-Crnuce, Spratly Islands Jerala-Strukelj, Zdenka, Mavcice, Spratly Islands
PATENT ASSIGNEE(S):	LEK, tovarna farmacevtskih in kemicnih izdelkov, d.d., Ljubljana, Ljubljana, Spratly Islands (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5519012		19960521
APPLICATION INFO.:	US 1994-357790		19941216 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1993-44509, filed on 9 Apr 1993, now abandoned		

	NUMBER	DATE
PRIORITY INFORMATION:	AT 1992-795	19920416

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Rollins, John W.
ASSISTANT EXAMINER:	Prats, Francisco C.
LEGAL REPRESENTATIVE:	Pollock, Vande Sande & Priddy
NUMBER OF CLAIMS:	10
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	42 Drawing Figure(s); 42 Drawing Page(s)
LINE COUNT:	1262

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Novel inclusion complexes of racemic 1,4-dihydropyridines and enantiomers thereof of the formula ##STR1## wherein R represents a phenyl group, substituted with nitro, trifluoromethyl, difluoromethoxy group or with one or two halo atoms (especially chlorine),

R.sub.1 and R.sub.2, if the same, represent methyl groups and if one of them has the meaning of a 2-aminoethoxymethyl or cyano group, the other represents a methyl group,

R.sub.3 and R.sub.4, if different, stand each time for a hydrogen, linear or branched C.sub.1 -C.sub.6 -alkyl, 2-methoxyethyl, 1-(phenylmethyl)-3-piperidinylphenyl, styryl, furyl, piperidino, 4-diphenylmethyl-1-piperazinylethyl, 5-phenyl-3-pirazolyloxy, 1-phenyl-methyl-3-pyrrolidinyl group or a group of the formula ##STR2## or, if the same, stand each time C.sub.1 -C.sub.4 alkyl group, and of acid addition salts thereof with methyl-.beta.-cyclodextrin, hydroxy-ethyl-.beta.-cyclodextrin or hydroxypropyl-.beta.-cyclodextrin, with the exception of inclusion complexes of racemic dihydropyridines with HP-.beta.-CD, or, in case of amlodipine and enantiomeric nicardipine, also with .beta.-cyclodextrin, are disclosed.

Whilst inclusion complexes of racemic dihydropyridines with the cites cyclodextrins are prepared in a well-known manner disclosed in the literature, enantiomerically pure dihydropyridines and inclusion complexes thereof with cyclodextrins are prepared in a novel way by means of preparative column chromatography.

The invention also relates to a pharmaceutical formulation containing novel inclusion complexes and to the use thereof as calcium antagonists for the treatment of hypertension, angina pectoris and cerebrovascular disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD TABLE IV

Review of reaction conditions and ability for preparing inclusion complexes of racemic and optically active DHP with different cyclodextrins

DHP	Enant. racemate	.beta.-CD	ME-.beta.-CD	HP-.beta.-CD	HE-.beta.-CD	solvent	Konc.DHP,CD (mol/l)	t/h/ T/.degree.C./ of solvent	elimination
MNA	(+), (-), R /	+	+	+		CH.sub.3 OH	0,05	1	reflux evaporation (65.degree. C.)
NC.HCl	(+), (-), R	+	+	+	+	H.sub.2 O	0,02-0,05	0.5-2	70.degree. C.

								lyophilisation
NTP	(+), (-), R							
	/	+	+	+	CH.sub.3 OH			
					0,05		0.1	
								room evaporation temp.
AML.S.								
	(+), (-), R							
		+	+	+	H.sub.2 O			
					0,02-0,08			
						1-2	70.degree. C.	
								lyophilisation
AML.A								
	(+), (-), R							
	/	+	+	+	CH.sub.3 OH			
					0,05	1	refl.	
								evaporation
							(65.degree. C.)	
KMNA	(+), (-), R							
	/	+	+	+	CH.sub.3 OH			
					0,05	1	refl.	
								evaporation
							(65.degree. C.)	
FDP	(+), (-), R							
	/	+	+	+	CH.sub.3 OH			
					0,02-0,07			
						1-2	refl.	
								evaporation
							(65.degree. C.)	

MNA = 2(N-benzyl-N-methyl-amino)ethyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydrpirydine-3,5-carboxylic acid
NH.HCl = nicardipine hydrochloride
NTP = nitrendipine
AML.**S** = **amlodipine** besylate
AML.A = ethyl2-[2aminoethoxy)methyl4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyidine-carboxylic acid
KMNA = ethyl1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridine-carboxyic acid
FDP = felodipine

L3 ANSWER 24 OF 28 USPATFULL on STN

ACCESSION NUMBER:	93:104967 USPATFULL
TITLE:	Method of treating impotence
INVENTOR(S):	Milne, Jr., George M., Niantic, CT, United States Wyllie, Michael G., Canterbury, England
PATENT ASSIGNEE(S):	Pfizer Inc., New York, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5270323		19931214
APPLICATION INFO.:	US 1993-31047		19930311 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1990-531494, filed on 31 May 1990, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Schenkman, Leonard		

LEGAL REPRESENTATIVE: Richardson, Peter C., Benson, Gregg C., Olson, A. Dean
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
LINE COUNT: 316
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of relieving erectile impotence in a human male. The method comprises administering to the male an erectile impotence relieving amount of a compound selected from the group consisting of U.K. 52,046, Amlodipine, Doxazosin and the pharmaceutically acceptable acid addition salts thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD TABLE 1

Comparative Effects In Monkeys

Drug	Threshold Dose	Tumescence	Rigidity	Time Course	Reversible
U.K.-52,046	0.1 .mu.g	+++	+++	S	S
Doxazosin	100 .mu.g	++	+	S	S
Papaverine	6.0 mg	++	++	S	S
Amlodipine	500 .mu.g	++	++	X	X
Phentolamine	1.5 mg	++	++	S	S

0 = no effect
+ = minimal effect
++ = good effect
+++ = full effect
S = satisfactory
X = unsatisfactory

L3 ANSWER 25 OF 28 USPAT2 on STN
ACCESSION NUMBER: 2004:39381 USPAT2
TITLE: Organic acid salt of amlodipine
INVENTOR(S): Cho, Seong Hwan, Suwon-si, KOREA, REPUBLIC OF
Youn, Yong Sik, Yongin, KOREA, REPUBLIC OF
Jung, Yun Taek, Seoul, KOREA, REPUBLIC OF
Park, Choong Sil, Icheon-si, KOREA, REPUBLIC OF
Lee, Hyuk Koo, Yongin-si, KOREA, REPUBLIC OF
Lee, Kwang Hyeg, Seongnam-si, KOREA, REPUBLIC OF
Jeong, Eun Ju, Chungcheongbuk-do, KOREA, REPUBLIC OF
Kim, Young Hoon, Seoul, KOREA, REPUBLIC OF
Jin, Hae Tak, Yongin-si, KOREA, REPUBLIC OF
Cheon, Jun Hee, Suwon-si, KOREA, REPUBLIC OF
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Jung, Sung Hak, Seoul, KOREA, REPUBLIC OF
Lim, Dong Kwon, Seongnam-si, KOREA, REPUBLIC OF
Yeon, Kyu Jeong, Yongin-si, KOREA, REPUBLIC OF
Kim, Yun Cheul, Seoul, KOREA, REPUBLIC OF
Park, Kyung Mi, Seoul, KOREA, REPUBLIC OF
Kang, Hyun Suk, Seoul, KOREA, REPUBLIC OF
PATENT ASSIGNEE(S): CJ Corp., Seoul, KOREA, REPUBLIC OF (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6756390	B2	20040629	
APPLICATION INFO.:	US 2003-628210		20030729	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	KR	20020730

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Owens, Amelia A.
LEGAL REPRESENTATIVE: Greenblum & Bernstein, P.L.C.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 446
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are a novel organic acid salt of amlodipine with superb physicochemical properties, its preparation method, and a pharmaceutical composition containing the same as a therapeutically active ingredient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM U.S. Pat. No. 6,291,490 introduces a pharmaceutical composition containing as an active ingredient **S**-(-)-**amlodipine** which possesses potent activity in treating both systolic and diastolic hypertension while avoiding adverse effects associated with administration of the racemic mixture of amlodipine.

L3 ANSWER 26 OF 28 USPAT2 on STN
ACCESSION NUMBER: 2003:38384 USPAT2
TITLE: Resolution of the enantiomers of amlodipine
INVENTOR(S): Zhang, Xitian, N. 159 Remin Street, Changchun, JiLin, CHINA 130022

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6646131	B2	20031111	
	WO 2001060799		20010823	
APPLICATION INFO.:	US 2002-203615		20020816	(10)
	WO 2000-CN538		20001208	

	NUMBER	DATE
PRIORITY INFORMATION:	CN 2000-102701	20000221

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Morris, Patricia L.
LEGAL REPRESENTATIVE: Jacobson Holman PLLC
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)

LINE COUNT: 184
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a feasible method for the separation of both (S)-(-)-enantiomer and (R)-(+)-enantiomer of racemic amlodipine with higher optically purity. The chiral reagent for separation is tartaric acid and the chiral auxiliary reagent is hexadeuterium dimethyl sulphoxide (DMSO-d.sub.6).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM (**S**)-(-)-**amlodipine** and its salts are long-acting calcium channel blockers, and are thus useful for the treatment of hypertension and angina and (**R**)-(+)-**amlodipine** also exhibits activity in the treatment or prevention of atherosclerosis. ##STR1##

SUMM The invention provides a feasible method for the separation of racemic amlodipine. The chiral reagent for separation is L-tartaric acid or D-tartaric acid and the chiral auxiliary reagent is hexadeuterium dimethyl sulphoxide (DMSO-d.sub.6), in the amlodipine and tartaric acid mole ratio of about 1:0.25. The resulting precipitate is (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 solvate or (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 solvate.

SUMM The above precipitate can further be treated to give (**R**)-(+)-**amlodipine** or (**S**)-(-)-**amlodipine**.

SUMM The crystalline precipitate constituent is (**S**)-(-)-**amlodipine**-hemi-tartrate-mono-DMSO-d.sub.6 solvate or **R**-(+)-**amlodipine**-hemi-tartrate-mono-DMSO-d.sub.6 solvate respectively.

DETD (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 Solvate and (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 Solvate From (R, **S**)-**amlodipine**
DETD To a stirred solution of 5 g (R, **S**)-**amlodipine** in 22.9 g DMSO-d.sub.6 was added a solution of 0.458 g D-tartaric acid (0.25 mole equivalents) in 22.9 g DMSO-d.sub.6. Precipitation began within one minute, and the resulting slurry was stirred at room temperature overnight. The solid was collected by filtration, washing with 20 ml acetone. It was then dried at 50 in vacuo overnight to give 2.36 g (68% of theoretical yield) (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 solvate, m.p. 158-160 (Found: C 50.81%, H(D) 7.09%, N 4.84%, C.sub.20H.sub.25N.sub.2O.sub.5Cl 0.5 C.sub.4H.sub.6O.sub.6 C.sub.2D.sub.6OS; Calc. for C 50.74%, H (D) 7.04%, N 4.90%), optical purity 99.9% d.e. by chiral HPLC.
DETD 0.44 g L-tartaric acid (0.25 mole equivalents) was added to the filtered fluid and stirred at room temperature overnight. The solid was collected by filtration, washing with 20 ml acetone. It was then dried at 50 in vacuo overnight to give 2.0 g (55% of theoretical yield) (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 solvate, m.p. 158-160, (Found: C 50.67%, H (D) 6.95%, N 4.90%, C.sub.20H.sub.25N.sub.2O.sub.5Cl 0.5 C.sub.4H.sub.6O.sub.6 C.sub.2D.sub.6OS: Calc. for C 50.74%, H (D) 7.04%, N 4.93%), optical purity 99.5% d. e. by chiral HPLC.
DETD (**S**)-(-)-**amlodipine** From (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 Solvate
DETD 5 g (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 solvate and 56 ml 2N NaOH water solution were stirred together with 56 ml CH.sub.2Cl.sub.2 for 40 minutes. The organic solution was separated off and washed with water. The CH.sub.2Cl.sub.2 was distilled

off and hexane was added and stirred to crystallize it. The solid was collected by filtration and dried at 50 in vacuo overnight to give 3.20 g (88% of theoretical yield) (**S**)-(-)-**amlodipine**, m.p. 107-110, (Found: C 58.69%, H 6.09%, N 6.84%; Calc. for C.sub.20H.sub.25N.sub.2O.sub.5Cl: C 58.75%, H 6.16%, N 6.85%), [ ].sub.D.sup.25-32.6 (C=1, MeOH), optical purity 99.9% e.e. by chiral HPLC.

DETD (**R**)-(+)-**amlodipine** From (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 Solvate

DETD 5 g (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 solvate and 56 ml 2N NaOH water solution were stirred together with 56 ml CH.sub.2Cl.sub.2 for 40 minutes. The CH.sub.2Cl.sub.2 was distilled off and hexane was added and stirred to crystallize it. The solid was collected by filtration and dried at 50

DETD in vacuo overnight to give 3.31 g (91% of theoretical yield) (**R**)-(+)-**amlodipine**, m.p. 107-110, (Found: C 58.41%, H 6.05%, N 6.62%; Calc. for C.sub.20H.sub.25N.sub.2O.sub.5Cl: C 58.75%, H 6.16%, N 6.85%), [ ].sub.D.sup.25+32.6 (C=1, MeOH), optical purity 99.5% e.e. by chiral HPLC.

DETD (**S**)-(-)-**amlodipine**-hemi-D-tartrate-mono-DMSO-d.sub.6 Solvate and **R**-(+)-**amlodipine**-hemi-L-tartrate-mono-DMSO-d.sub.6 Solvate From (R, **S**)-**amlodipine**.

DETD The method of example 1 was used, but substituting the DMSO-d.sub.6 with a mixed solvent and DMSO-d.sub.6/amlodipine 1 (mole ratio). V.sub.solvent/(V.sub.DMSO-d6+V.sub.solvent) was shown in percentages. (V.sub.DMSO-d6+V.sub.solvent)M=4.about.18, in which, V, volume, ml; solvent; M, mass of amlodipine, g. The solvate can then be processed to (**S**)-(-)-**amlodipine** and (**R**)-(+)-**amlodipine** according to the procedures of examples 2 and 3.

DETD Benzene Sulfonic Acid (**S**)-(-)-**amlodipine**

DETD 5 g (**S**)-(-)-**amlodipine** was put into 120 ml water and 1.4 g benzene sulfonic acid was added and stirred, which was heated to 60 under protection of nitrogen. After dissolution, with stirring stopped, the solution was cooled to room temperature and then crystallized overnight. The solid was collected by filtration, washing with 20 ml water, and then the benzene sulfonic acid (**S**)-(-)-**amlodipine** was dried at 50 in vacuo overnight to give 6.2 g (90% of theoretical yield), (Found: C 54.85%, H 5.15%, N 5.58%; Calc. for C.sub.20H.sub.25N.sub.2O.sub.5Cl: C 54.72%, H 5.14%, N 5.34%), [ ].sub.D.sup.25-24.9 (C=1, MeOH), optical purity 99.9% e.e. by chiral HPLC.

DETD The invention provides a feasible method for the separation of racemic amlodipine, which uses hexadeuterium dimethyl sulphoxide as the chiral auxiliary reagent to separate the enantiomers of racemic amlodipine with a time separation in optical purities of up to 100% e.e. and in yield of up to 68%, this high pure (**S**)-(-)-**amlodipine** is higher security for patients. Hexadeuterium dimethyl sulphoxide is reclaimed without notable cost augment for its wastage, so susceptible of industrial application.

CLM What is claimed is:

1. A method for the separation of (R)-(+)- and (S)-(-)-isomers of amlodipine from mixtures thereof, which comprises the reaction of the mixture of isomers with D- or L-tartaric acid as a chiral reagent, wherein the mole ratio of tartaric acid to amlodipine is 0.25, in a) hexadeuterium dimethyl sulphoxide (DMSO-d.sub.6) or b) an organic solvent containing DMSO-d.sub.6 for precipitation of, respectively, a DMSO-d.sub.6 solvate of D-tartrate salt of (**S**)-(-)-**amlodipine**, or a DMSO-d.sub.6 solvate of a L-tartrate salt of (**R**)-(+)-**amlodipine**.

4. The method according to claim 2, wherein the solvate precipitated is,

respectively, (**S**)-(-)-**amlodipine**-hemp-D-tartrate-mono-DMSO-d.sub.6-solvate or (**R**)-(+)-**amlodipine**-hemi-L-tartrate-mono-DSMO-d.sub.6-solvate.

L3 ANSWER 27 OF 28 USPAT2 on STN

ACCESSION NUMBER:	2002:157675 USPAT2		
TITLE:	Mutual prodrug of amlodipine and atorvastatin		
INVENTOR(S):	Crook, Robert James, Sandwich, UNITED KINGDOM Pettman, Alan John, Sandwich, UNITED KINGDOM		
PATENT ASSIGNEE(S):	Pfizer, Inc., New York, NY, United States (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6737430	B2	20040518
APPLICATION INFO.:	US 2001-985		20011031 (10)
	NUMBER		DATE
PRIORITY INFORMATION:	GB 2000-27410		20001109
	US 2000-255025P		20001212 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Morris, Patricia L.		
LEGAL REPRESENTATIVE:	Richardson, Peter C., Benson, Gregg C., Samuels, Lisa A.		
NUMBER OF CLAIMS:	21		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)		
LINE COUNT:	1002		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to a mutual prodrug of amlodipine and atorvastatin, pharmaceutically acceptable acid addition salts thereof, pharmaceutical compositions thereof and the use of said prodrug and its salts in the manufacture of medicaments for the treatment of atherosclerosis, angina pectoris, combined hypertension and hyperlipidaemia and the management of cardiac risk.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD A solution of **R**(-)-**amlodipine** (840 mg, 2 mmol) and atorvastatin free acid (predominantly as the lactone) (1 g, 1.8 mmol) in ethanol (30 ml) was refluxed for 18 hours. The solvent was then evaporated in vacuo and the resulting oil purified by column chromatography using a standard silica column and eluting with 100% dichloromethane changing to 95%/5% dichloromethane/methanol. The desired product was obtained as a white foam (1.35 g, 76%). NMR (DMSO) d: 1.16-1.19 (t, 3H), 1.38-1.48 (m, 2H), 1.42-1.46 (d, 6H), 1.60-1.68 (m, 2H), 2.23-2.37 (d, 2H), 2.36 (s, 3H), 3.25-3.32 (m, 1H), 3.32-3.36 (m, 2H), 3.52-3.56 (m, 2H), 3.58-3.65 (m, 1H), 3.80-3.98 (m, 2H), 3.91-3.93 (m, 1H), 3.56 (s, 3H), 4.00-4.02 (m, 2H), 4.59-4.69 (d, 2H), 4.65 (s, 1H), 4.77 (s, 1H), 5.36 (s, 1H), 7.02-7.05 (m, 1H), 7.07-7.14 (m, 5H), 7.15-7.18 (m, 1H), 7.22-7.25 (m, 2H), 7.25-7.28 (m, 1H), 7.29-7.32 (m, 2H), 7.26-7.3 (m, 2H), 7.3-7.32 (m, 1H), 7.37-7.39 (m, 1H), 7.54-7.58 (d, 2H), 7.97 (t, 1H), 8.47 (s, 1H), 9.76 (s, 1H). MS (ESI): m/z [MNa.sup.+] 971.5 Na.sup.+ requires 971.5.

DETD A solution of **S**(+)-**amlodipine** (840 mg, 2 mmol) and atorvastatin free acid (predominantly as the lactone) (1 g, 1.8 mmol) in ethanol (30 ml) was refluxed for 18 hours. The solvent was then evaporated in vacuo and the resulting oil purified by column chromatography using a standard silica column and eluting with 100%

dichloromethane changing to 95%/15% dichloromethane/methanol. The desired product was obtained as a white foam (1.14 g, 64%). NMR (DMSO) d: 1.16-1.19 (t, 3H), 1.38-1.48 (m, 2H), 1.42-1.46 (d, 6H), 1.60-1.68 (m, 2H), 2.23-2.37 (d, 2H), 2.36 (s, 3H), 3.25-3.32 (m, 1H), 3.32-3.36 (m, 2H), 3.52-3.56 (m, 2H), 3.58-3.65 (m, 1H), 3.80-3.98 (m, 2H), 3.91-3.93 (m, 1H), 3.56 (s, 3H), 4.00-4.02 (m, 2H), 4.59-4.69 (d, 2H), 4.65 (s, 1H), 4.77 (s, 1H), 5.36 (s, 1H), 7.02-7.05 (m, 1H), 7.07-7.14 (m, 5H), 7.15-7.18 (m, 1H), 7.22-7.25 (m, 2H), 7.25-7.28 (m, 1H), 7.29-7.32 (m, 2H), 7.26-7.3 (m, 2H), 7.3-7.32 (m, 1H), 7.37-7.39 (m, 1H), 7.54-7.58 (d, 2H), 7.97 (t, 1H), 8.47 (s, 1H), 9.76 (s, 1H). MS (ESI): m/z [MNa.sup.+] 971.4 Na.sup.+ requires 971.5.

L3 ANSWER 28 OF 28 USPAT2 on STN

ACCESSION NUMBER:	2002:141545 USPAT2
TITLE:	Methods of pharmacological treatment using **S** (-) **amlodipine**
INVENTOR(S):	Foster, Robert T., Edmonton, CANADA
PATENT ASSIGNEE(S):	Isotechnika, Inc., Alberta, CANADA (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6476058	B2	20021105
APPLICATION INFO.:	US 2001-987661		20011115 (9)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1999-433963, filed on 4 Nov 1999, now patented, Pat. No. US 6333342		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-107007P	19981104 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Criares, Theodore J.
ASSISTANT EXAMINER:	Kim, Jennifer
LEGAL REPRESENTATIVE:	Burns, Doane, Swecker & Mathis, LLP
NUMBER OF CLAIMS:	5
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT:	984

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Methods and compositions are disclosed utilizing the optically pure S(-) isomer of amlodipine. This compound is a potent drug for the treatment of hypertension while avoiding the concomitant liability of adverse effects associated with the administration of the racemic mixture of amlodipine. The S(-) isomer of amlodipine is also useful for the treatment of angina and such other conditions as may be related to the activity of **S**(-) **amlodipine** as a calcium channel antagonist without the concomitant liability of adverse effects associated with the racemic mixture of amlodipine.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Methods of pharmacological treatment using **S**(-) **amlodipine**

AB Methods and compositions are disclosed utilizing the optically pure S(-) isomer of amlodipine. This compound is a potent drug for the treatment of hypertension while avoiding the concomitant liability of adverse effects associated with the administration of the racemic mixture of amlodipine. The S(-) isomer of amlodipine is also useful for the treatment of angina and such other conditions as may be related to the activity of **S**(-) **amlodipine** as a calcium channel antagonist without the concomitant liability of adverse effects

associated with the racemic mixture of amlodipine.

SUMM Pharmacological therapy utilizing pure formulations of **S**(-) **amlodipine** results in effective theraputic results while avoiding toxicities and adverse effects of racemic amlodipine. The methods and compositions described include the enriched deuterated forms of amlodipine as well as the nonenriched form. Amlodipine and deuteroamlodipine have a chiral center at C4 in the dihydropyridine ring, and thus can exist as optical isomers. The isomers may be separated by various methods, for example selective crystallization and column chromatography. See for example T. Shibanuma, et al., Chem. Pharm. Bull., 28, 2809-2812 (1980). Alternatively, **S**(-) **amlodipine** may be prepared using optically active reactants, or by a combination of separation and chiral synthesis. Optical isomers of compounds are specified (+) or (-), indicating the direction the chiral center rotates a plane of polarized light.

SUMM The present commercial formulation of amlodipine contains the drug as the salt; amlodipine besylate. The term "amlodipine" herein refers to amlodipine and its pharmaceutically suitable salts and esters including amlodipine besylate and deuterated amlodipine and its pharmaceutically acceptable salts and esters including deuterated amlodipine besylate. This isomer will hereinafter be referred to as **S**(-) **amlodipine**. The terms "**S**(-) **amlodipine**" and "S(-) isomer of amlodipine" as used herein includes substantially optically pure **S**(-) **amlodipine** as well as optically pure **S**(-) **amlodipine**.

SUMM The methods and compositions of the present invention utilize the discovery that the optically pure S(-) isomer of amlodipine is an effective antihypertensive agent for both systolic and diastolic hypertension, particularly in mild to moderate disease and angina, which avoids the adverse effects including but not limited to headache and edema, dizziness, flushing, palpitation, fatigue, nausea, abdominal pain and somnolence which are associated with the administration of the racemic mixture of amlodipine. It has also been discovered that these novel compositions of matter containing optically pure **S**(-) **amlodipine** are useful in treating other conditions as may be related to the activity of **S**(-) **amlodipine** as a calcium channel antagonist, including but not limited to cerebral ischemia, cerebral disorders, arrhythmias, cardiac hypertrophy, heart failure, coronary vasospasm, myocardial infarction, renal impairment, viral infection, thrombosis, atherosclerosis, peripheral vascular disease, migraine headache, restenosis following vascular surgery or injury and acute renal failure while avoiding the above-described adverse effects associated with the administration of the racemic mixture of amlodipine. The present invention also includes methods for treating the above-described conditions in a human while avoiding the adverse effects that are associated with the racemic mixture of amlodipine by administering the S(-) isomer of amlodipine to said human.

DETD The present invention encompasses a method of treating hypertension in a human while avoiding the concomitant liability of adverse effects associated with the racemic mixture of amlodipine, which comprises administering to a human in need of such anti-hypertensive therapy, an amount of **S**(-) **amlodipine** or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate hypertension, but insufficient to cause said adverse effects associated with administration of racemic amlodipine.

DETD The present invention also encompasses an pharmaceutical composition for treatment of hypertension, in a human in need of anti-hypertensive

therapy, which comprises an amount of **S**(-) **amlodipine** or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate hypertension but insufficient to cause adverse effects of racemic amlodipine. The calcium channel blocking composition may optionally contain a pharmaceutically acceptable carrier.

DETD The present invention further encompasses a method of treating angina in a human, while avoiding the concomitant liability of adverse effects associated with the administration of racemic amlodipine, which comprises administering to a human in need of anti-angina therapy, an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate angina but insufficient to cause said adverse effects associated with administration of racemic amlodipine.

DETD In addition, the present invention encompasses an pharmaceutical composition for the treatment of a human having angina, which comprises an amount of **S**(-) **amlodipine** or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate angina but insufficient to cause adverse effects associated with the administration of racemic amlodipine. The antianginal composition may optionally contain a pharmaceutically acceptable carrier.

DETD A further aspect of the present invention includes a method of treating a condition caused by excessive calcium influx in cells in a human, while avoiding the concomitant liability of adverse effects associated with the administration of racemic amlodipine, which comprises administering to a human in need of a reduction in excessive calcium influx, an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate or prevent excessive calcium influx in cells but insufficient to cause said adverse effects associated with the administration of racemic amlodipine. Conditions caused by excessive calcium influx in cells in a human include, but are not limited to, cerebral ischemia, cerebral disorders such as cognitive disorders including but not limited to Alzheimer's dementia and memory impairment, retinal ischemia, viral infection, thrombosis, atherosclerosis, arrhythmias, cardiac hypertrophy, congestive heart failure, coronary vasospasm, migraine, bronchospasm and asthma, Raynaud's phenomenon, myocardial infarction, renal impairment, restenosis following vascular surgery or injury and acute renal failure.

DETD The invention also includes a pharmaceutical composition for treating a condition caused by excessive calcium influx in cells in a human, which comprises an amount of **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, said amount being sufficient to alleviate said condition but insufficient to cause adverse effects associated with the administration of racemic amlodipine. This pharmaceutical composition may optionally contain a pharmaceutically acceptable carrier.

DETD The term "substantially free of its R(+) stereoisomer" as used herein means that the composition contains a greater proportion or percentage of the S(-) isomer of amlodipine in relation to the R(+) isomer of amlodipine, said percentage being based on the total amount of amlodipine in the composition. In a preferred embodiment the term "substantially free of its R(+) stereoisomer" means that the composition contains at least 90% by weight of **S**(-) **amlodipine**, and 10% by weight or less of **R**(+) **amlodipine**. In the most preferred embodiment the term "substantially free of the R(+) stereoisomer" means that the composition contains at least 99% by weight **S**(-) **amlodipine**, and 1% or less of **R**(+) **amlodipine**. In another preferred embodiment the term

"substantially free of its R(+) stereoisomer" as used herein means that the composition contains about 100% by weight of **S**(-) **amlodipine**. The terms "substantially optically pure S(-) isomer of amlodipine" and "optically pure S(-) isomer of amlodipine" are also encompassed by the above-described meanings.

DETD Optically pure **S**(-) **amlodipine** can be prepared in a number of ways. Among these methods, the resolution of a racemic mixture of amlodipine or its precursors and the asymmetric synthesis of amlodipine or precursors thereof are particularly useful. Resolution of a racemic mixture by fractional crystallization of diastereomeric derivatives or salts is perhaps the most straightforward method for obtaining optically pure **S**(-) **amlodipine**.

DETD Amlodipine is a basic compound and therefore diastereomeric salts suitable for separation by fractional crystallization are readily formed by the addition of chiral acid resolving agents in optically pure form to racemic amlodipine. Suitable resolving agents for use here include optically pure tartaric acid and its derivatives, camphorsulfonic acid, mandelic acid and derivatives thereof, and other optically active acids. The desired **S**(-) **amlodipine** isomer may be recovered either from the crystallized diastereomer or from the mother liquor, depending on the solubility properties of the particular acid resolving agent employed and depending on the particular acid enantiomer used. The identity of the **S**(-) **amlodipine** isomer so obtained may be confirmed by polarimetry and other analytical methods.

DETD A particular preferred means of obtaining **S**(-) **amlodipine** is based on the fractional crystallization of diastereomeric mixtures formed by basic resolving agents and racemic carboxylic-acid-containing precursors of amlodipine. See, for example, T. Shibanuma et al., Chem. Pharm. Bull. 28(9): 2809-2812 (1980) (who resolved the structurally related dihydropyridine nicardipine) and M. Eltze et al., Chirality 2: 233-240 (1990) and references cited therein. In particular, **S**(-) **amlodipine** is obtained by means of resolution of the corresponding racemic 4-aryl-1-ethoxymethyl-1,4-dihydro-5-methoxycarbonyl-2,6-dimethylpyridine-3-carboxylic acids by means of crystallization of the diastereomeric salts formed upon addition of basic resolving agents to the racemic precursor-followed by subsequent alkylation and esterification as described in International Patent Applications WO 88/07524 and WO 88/07525, Byk Gulden, 1988. Optically pure cinchonine and cinchonidine salts are basic resolving agents that have proven useful in the resolution of the dihydropyridines including amlodipine.

DETD The chemical synthesis of the racemic mixture of amlodipine can be performed by the method described in U.S. Pat. Nos. 4,572,909 and 5,438,145 as well as by other means known to those skilled in the art. The racemic acid ester is converted to its cinchonidine salt in methanol solution. Upon dilution with water and standing at room temperature, a crystalline precipitate is formed which can be subsequently recrystallized to constant rotation to give the diastereomerically pure cinchonidine salt. Further, the mother liquids from the original crystallization can be reduced in volume and stirred at room temperature, e.g., overnight, to afford a fine precipitate which can also be recrystallized to give the diastereomerically pure cinchonidine salt. The cinchonidine salt is partitioned between ethyl acetate and dilute hydrochloric acid to liberate the enantiomerically pure acid. The acid is then esterified using carbonyldiimidazole (CDI) and ethanolic sodium ethoxide, yielding **S**(-) **amlodipine**.

DETD In one embodiment of the present method, the optically pure S(-) isomer of amlodipine is administered to an individual suffering from hypertension. For example, **S**(-) **amlodipine** is administered therapeutically to an individual to reduce or ameliorate hypertension. In another embodiment, optically pure **S**(-)

amlodipine can be administered prophylactically to reduce the probability of occurrence of hypertension.

DETD **S**(-) **amlodipine** and its pharmaceutically acceptable salts and esters and deuterated amlodipine and pharmaceutically salts and esters of the present invention can be used to prepare pharmaceutical compositions useful in the treatment of the diseases and conditions discussed above. In these treatment regimens, a therapeutic amount of **S**(-) **amlodipine** (salts, esters and deuterated derivatives) can be administered in admixture with a pharmaceutically acceptable non-toxic carrier. A therapeutically effective amount is that amount which, when administered to a mammal in need thereof, is sufficient to effect treatment, as defined above. Thus, the level of the drug in the formulation can vary from about 5 percent weight (%w) to about 95%w of the drug based on the total formulation and about 5%w to 95%w excipient. Preferably the drug is present at a level of about 10%w to about 70%w.

DETD In the practice of the above described method of the present invention a therapeutically effective amount of the **S**(-) **amlodipine** or a pharmaceutical composition containing same is administered via any of the usual and acceptable methods known in the art, either singly or in combination with other pharmaceutical agents. These compounds or compositions can thus be administered orally, systemically (e.g., transdermally, intranasally or by suppository) or parenterally (e.g., intramuscularly, subcutaneously and intravenously), and can be administered either in the form of solid or liquid dosages including tablets, solutions, suspensions, aerosols, and the like, as discussed in more detail above. It is preferred to administer **S**(-) **amlodipine** orally.

DETD The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids. Optionally, ester analogues of **S**(-) **amlodipine** may be used in the present invention.

CLM What is claimed is:

1. A method for blocking calcium channels, while avoiding the concomitant liability of adverse effects associated with administration of racemic amlodipine, which comprises administering to an animal in need of calcium channel blocking therapy, an amount of deuterated **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of its R(+) stereoisomer, wherein the deuterated **S**(-) **amlodipine** or salt thereof, comprises an amlodipine selected from the genus described by: ##STR2## wherein R represents either hydrogen or deuterium; and wherein R.sup.1 represents either hydrogen or deuterium, and at least one of the R or R.sup.1 is deuterium, said amount being sufficient to provide calcium channel blockade but insufficient to cause said adverse effects of racemic amlodipine.

3. A compound comprising deuterated **S**(-) **amlodipine**, or a pharmaceutically acceptable salt thereof, substantially free of the R(+) stereoisomer, wherein the deuterated **S**(-) **amlodipine** or salt thereof, comprises an amlodipine selected from the genus described by: ##STR3## wherein R represents either hydrogen or deuterium; and wherein R.sup.1 represents either hydrogen or deuterium, and at least one of the R or R.sup.1 is deuterium.

5. The pharmaceutical composition of claim 4 wherein the composition contains at least 99% by weight **S**(-) **amlodipine** and 1% or less **R**(+) **amlodipine** based on the total amount of amlodipine in the composition.